

**THE INTENSIVE CARE OF PATIENTS
FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION**

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CHAPTER 11

ANALGESIA: MORPHINE

Morphine (7, 8, Didehydro 4, 5, epoxy 17, methyl morphinan, 3, 6 Diol) is a major component of the juice obtained from the poppy, *Papaver Somniferum*. Morphine and its congeners have long been known for their psychological and analgesic properties. Since its description on tablets of stone by the Sumerian tribe in 4,600 BC, other ancient civilisations including the Egyptians, the Assyrians and the Greeks in the 4th Century BC have used it. Many of the early physicians also used the drug. Hippocrates prescribed poppy wine and thought it particularly useful for uterine infections. In the 6th Century AD the Arabs took it to Persia where it rapidly became popular as a recreational drug and the great physician Avicenna died in 1037 from opium intoxication. During the 16th Century it was in widespread use in Europe and Paracelsus had such a high opinion of this drug that he named it Laudanum. Thomas Sydenham was attributed with its introduction to the United Kingdom in 1680. A century later, the British introduced it into China, where they bartered tea for opium. This eventually led to the "Opium War" between the two countries, part of the settlement of which was Britain being given Hong Kong for the next 150 years. Friedrich Sertefner isolated the active constituent of poppy juice in 1806 and named it morphine after the



Greek god of dreams, Morpheus. It was freely used in the American civil war and produced many addicts. In 1925 Gulland and Robinson identified its structure.

Metabolism of Morphine

In man morphine is principally metabolised by the microsomal enzyme UDP-glucuronyl transferase (UDP GT), mostly to glucuronides. The principal metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Choonara and his colleagues (1989) have demonstrated that in premature infants the clearance of morphine is reduced compared with children. However, they also noted the M3G/morphine ratio in plasma and urine and M6G/morphine ratio in urine were higher in children than in neonates, suggesting the enhancement of glucuronidation pathways with growth. Since there was no difference in the M3G/M6G ratio between children and neonates, they also suggested that both glucuronidation pathways develop in a similar fashion. In addition to M3G and M6G other metabolic pathways may generate small amounts of normorphine. The principal metabolic pathways are shown in Figure 11.1.

In common with many acidic drugs morphine is bound to albumin and decreases in the concentration of this plasma protein will give rise to an increased free drug fraction.

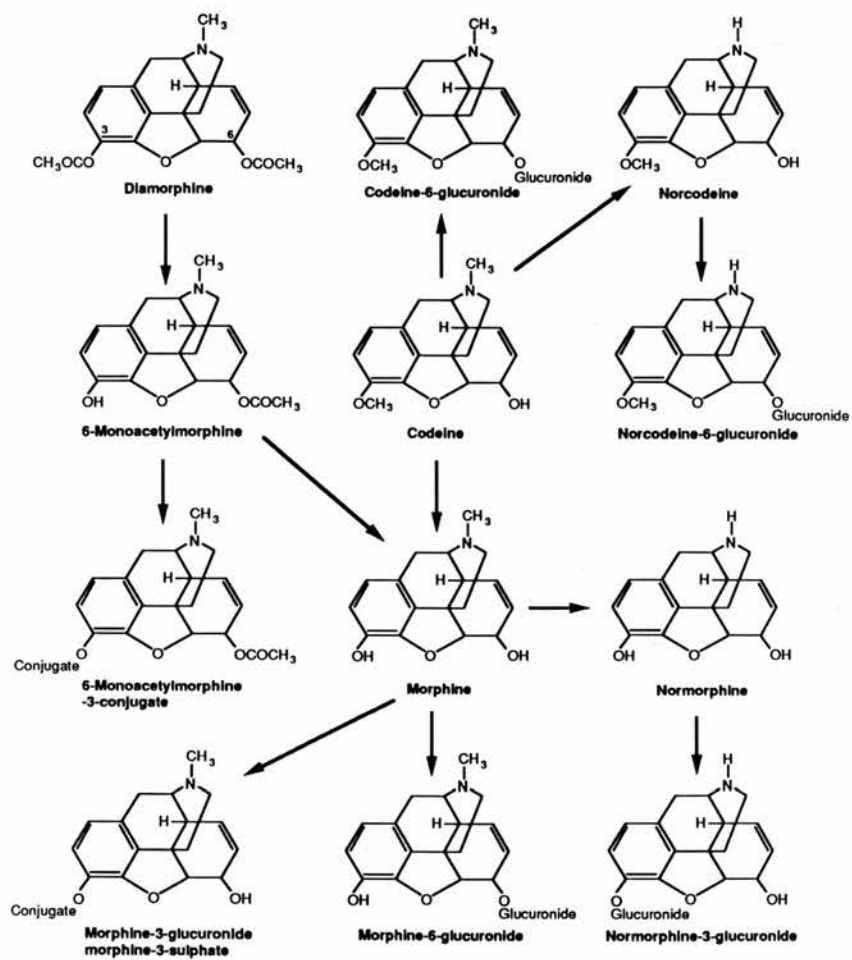


Figure 11.1: The principal metabolic pathways of morphine.

Morphine is metabolised by the liver, so a decrease in hepatic blood flow leads to a reduction in clearance and a prolonged effect of the drug can be expected. In addition, changes in the pH of blood will also give rise to alterations in the amount of free drug available (Finck et al 1977).

Methods Used to Measure Morphine and Its Metabolites

Three methods have been used in the studies described in this chapter to assay morphine, M3G and M6G. In the first studies (1983-1985) the radioimmunoassay (RIA) method described by the Oxford group (Moore et al 1984a) was used exclusively, but was found to cross-react with metabolites which limited its usefulness. High performance liquid chromatography (HPLC) became available in 1985, enabling the accurate quantification of measurement of morphine and its metabolites M3G and M6G. In 1988 Quinn and his colleagues developed the extracted radioimmunoassay method which removes the cross-reacting metabolites from the plasma before measurement of morphine concentration. The latter method is more sensitive than HPLC and takes less time to perform. Newer radioimmunoassays developed to measure M3G and M6G have not been utilised for studies in this thesis. Details of the assays used for this thesis are shown in Table 11.1.

Analytical Technique	Morphine	M3G	M6G
RIA (Moore et al 1984)	1	1	1
LSE-RIA (Quinn et al 1988)	1	0	0
HPLC (Svennson 1982)	2	10	2

Table 11.1: Sensitivity of morphine, M3G and M6G assays (ng/ml). LSE = liquid/solid extraction

MORPHINE AND LIVER DISEASE

Since morphine has long been thought to be metabolised in the liver, diseases of this organ could be expected to decrease elimination and alter the disposition of morphine. However, studies in patients with liver disease have given conflicting results. Patwardhan and his colleagues (1981) studied six patients with moderate to severe cirrhosis and demonstrated normal elimination of morphine. When this study was repeated using two RIA methods, one specific for morphine and the other cross reacting with morphine and its metabolites, an increase in elimination half life due to a decrease in clearance was demonstrated (Mazoit et al 1984). Anaesthesia and surgery, by changing hepatic blood flow, could also be expected to produce further changes. With the widespread use of this drug it is therefore surprising that so little information is available on the disposition of morphine in patients following liver surgery. One of the aims of part of this thesis was therefore to try and improve our knowledge in this area and resolve some of the controversies.

Two of the studies in this chapter have been submitted by Mr K Quinn as part of a PhD thesis to the University of Cambridge entitled "The Pharmacokinetics and Drug Metabolism of Morphine in Man". This work is identified in the text with his name. I acted as his supervisor.

STUDIES IN PATIENTS DURING AND AFTER

LIVER TRANSPLANTATION

The first study, performed on patients immediately on arrival in the intensive care unit, after liver transplantation, attempted to define the pharmacokinetics of morphine. The analyses was performed by Napp Laboratories Ltd., Cambridge.

MORPHINE PHARMACOKINETICS IN PATIENTS

FOLLOWING LIVER TRANSPLANTATION

Advances in the management of chronic pain. (1986) 109-112

Patients and Methods

Five patients were studied on return to the Intensive Care Unit when cardiorespiratory stability had been achieved and the blood loss was minimal, usually within one hour of return to the intensive care unit. A slow intravenous injection of morphine sulphate (2.5 mg) was administered, following which blood, urine and bile were sampled at intervals of 30 mins for 6hrs and then at 12, 18 and 24hrs from the start of the study. Analysis of the plasma and urine was performed using radioimmunoassay (Moore et al 1984a).

Results

Five female patients, age 35 (22-49) years, weight 51 (36-65) kg [mean (range)] completed the study. Three patients had primary biliary cirrhosis, one fulminant

hepatitis A and the final patient underwent retransplantation for rejection. Their biochemical parameters and the and ischaemic time of the donor liver are shown in Table 11.2. Individual plasma morphine levels are shown in Figure 11.2.

After the initial increase, a second peak or plateau of morphine levels is seen approximately 3 hours after administration of the morphine. Plasma concentrations of morphine then decreased to undetectable levels by 12 hours. Urine concentrations of morphine, shown for an individual patient in Figure 11.3, follow the same pattern as plasma levels but at far greater values.

Discussion

A previous study in patients following renal transplantation also demonstrated a plateau of plasma morphine levels occurring at approximately the same time but not in normal subjects (Moore et al 1984b). Second peaks have been described with other opiates (Stoeckel, Hengstmann and Schuttler 1979; Isherwood et al 1984).

Patient	Biliirubin ($\mu\text{mol/l}$)	ALT (U/l)	Prothrombin Time (seconds above control)	Alkaline Phosphatase (U/l)	Creatinine Clearance (mls/min)	Ischaemic Time (mins)
AM	98	297	4	91	<100	260
AB	180	1000	5	452	<100	174
JT	268	384	5	150	<100	297
BG	138	99	2	159	<100	279
DW	470	110	4.5	145	<100	359
Mean	230.8	378	4.1	199.4	<100	273.8

Table 11.2: Biochemical parameters and hepatic ischaemia time in five patients undergoing liver transplantation.

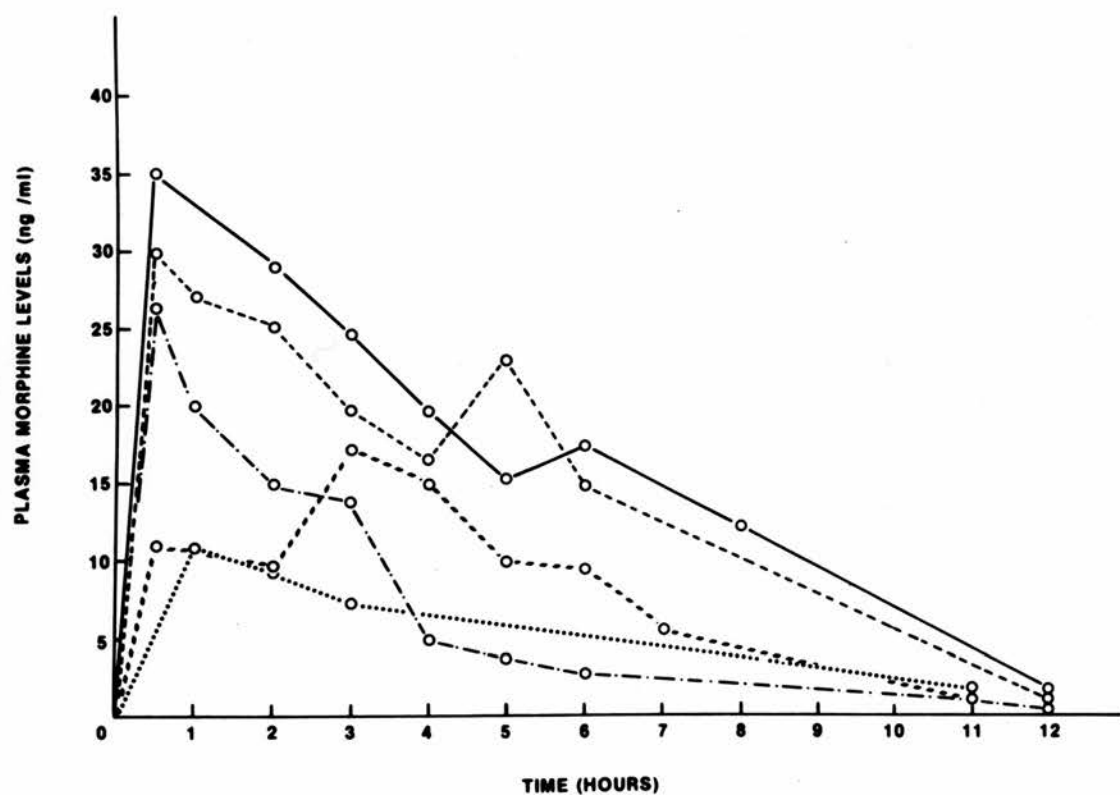


Figure 11.2: Plasma morphine concentrations in 5 patients following a single IV dose of 2.5mg morphine administered following liver transplantation.

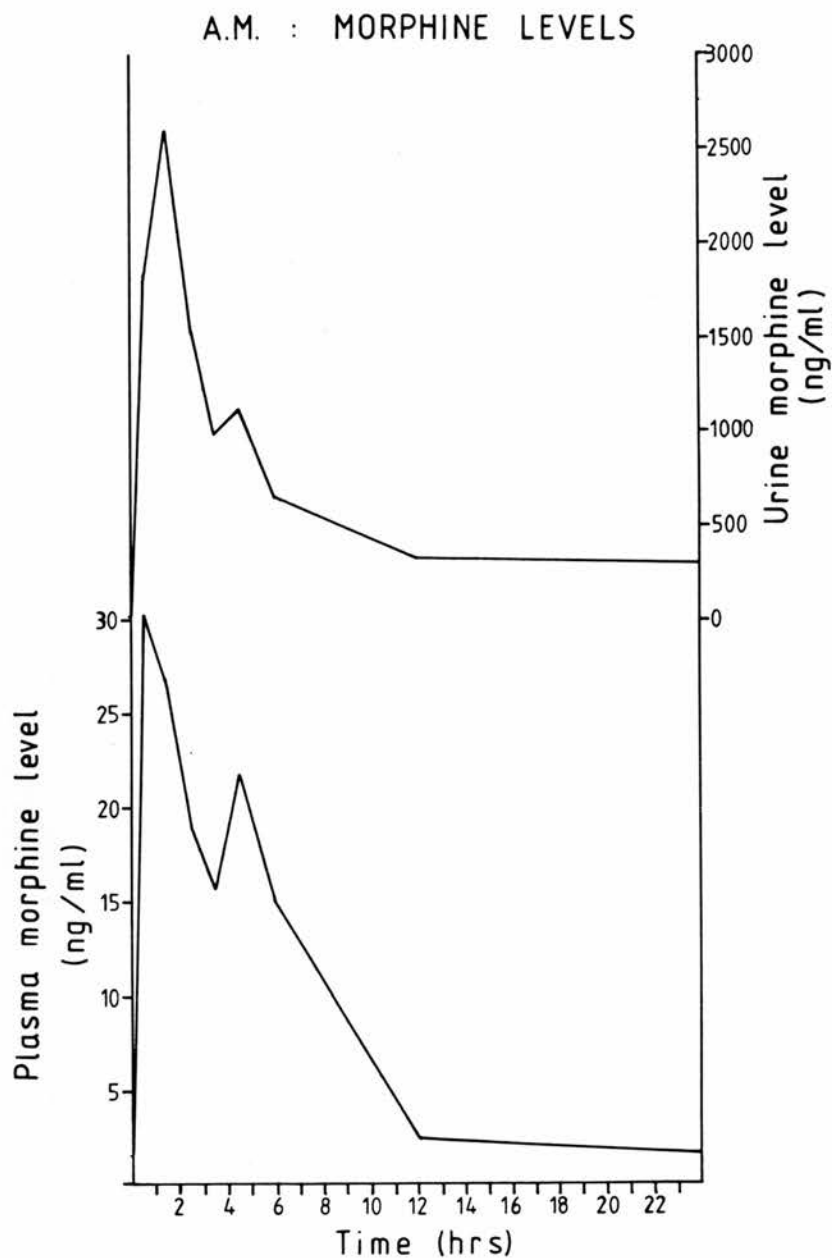


Figure 11.3: Simultaneous plasma and urinary concentrations of morphine in one patient after 2.5 mg morphine IV.

Several mechanisms for the appearance of second peaks following the administration of opiates have been suggested. These include enterohepatic recirculation (Hanks and Wand 1989) and gastric secretion of opiates (Stoeckel, Hengstmann and Schuttler 1979). Both of these mechanisms were felt to be unlikely in this group of patients since bile is drained from the T tube and most gastric contents will be aspirated by the nasogastric tube.

In an attempt to establish the mechanism of second peaks, a study was undertaken in children with biliary atresia, to see if second peaks occurred when biliary drainage is grossly impaired. Initially this was a pilot study and it was planned to investigate 6 children but only 2 were studied before the trial was discontinued.

I was assisted with the sample collection by Dr Maire P Shelly and with the sample analysis by Mr E Cory (Napp Laboratories Ltd).

***MORPHINE PHARMACOKINETICS IN PAEDIATRIC PATIENTS
BEFORE AND AFTER LIVER TRANSPLANTATION***

British Journal of Anaesthesia (1986) 58; 1218-1223

Patients and Methods

Informed consent was obtained from the parents of two children about to undergo orthotopic liver

transplantation. The preoperative details of the two patients are summarised in Table 11.3. Both children had end stage liver failure unresponsive to other medical and surgical treatment. One had congenital biliary atresia, the other cholestatic jaundice following neonatal hepatitis; both had secondary biliary cirrhosis. Renal function in both patients was thought to be normal preoperatively but in retrospect, patient 2 had unrecognised renal impairment at this time. Her plasma urea was raised although her plasma creatinine was normal, reflecting loss of muscle bulk due to her severe liver disease.

Anaesthesia was induced and maintained as described previously. Following induction of anaesthesia, a baseline blood sample was taken and 1mg/Kg morphine was administered intravenously as part of the anaesthetic technique. Blood samples were then taken at 5, 10, 15, 20, 30, 40, 50, 60 minutes after morphine administration while infusion and monitoring lines were being placed but before major surgery commenced. Blood removed for sampling was replaced by blood transfusion to maintain fluid balance. Further blood samples were taken from each child postoperatively.

	Patient 1	Patient 2
Age (years)	3.5	2.5
Sex	M	F
Weight (Kg)	14.0	7.5
Diagnosis	CNH	BA
Bilirubin		
($\mu\text{mol/l}$)	372	320
Alkaline Phosphatase		
(U/l)	1430	2390
Urea (mmol/l)	2.2	12.1
Creatinine		
($\mu\text{mol/l}$)	<100	60

Table 11.3: details of two paediatric patients before liver transplantation. CNH = Congenital Neonatal hepatitis. BA = Biliary Atresia.

High performance liquid chromatography had recently become available, allowing the estimation of plasma morphine, M3G and M6G concentrations. Recovery from plasma for all three compounds was greater than 90%.

Pharmacokinetic parameters were determined using ESTRIP (Brown and Manno, 1978) to estimate terminal slopes. Clearance was calculated as dose divided by the area under the curve, where AUC was estimated from the data points by the linear or logarithmic trapezoidal method and extrapolated to infinity. Volume of distribution at steady state was calculated as $D \cdot AUMC / AUC$, where AUMC is the area under the first moment curve again extrapolated to infinity.

Clinical and biochemical parameters of the patients' conscious level and liver and renal function as well as their opiate requirement, were recorded before and after surgery.

Results

The plasma concentrations of morphine, M3G and M6G for both patients are shown in Figure 11.4. During the hour after induction of anaesthesia but before major surgery, the plasma concentration of morphine increased initially to high levels, then decreased rapidly in both patients.

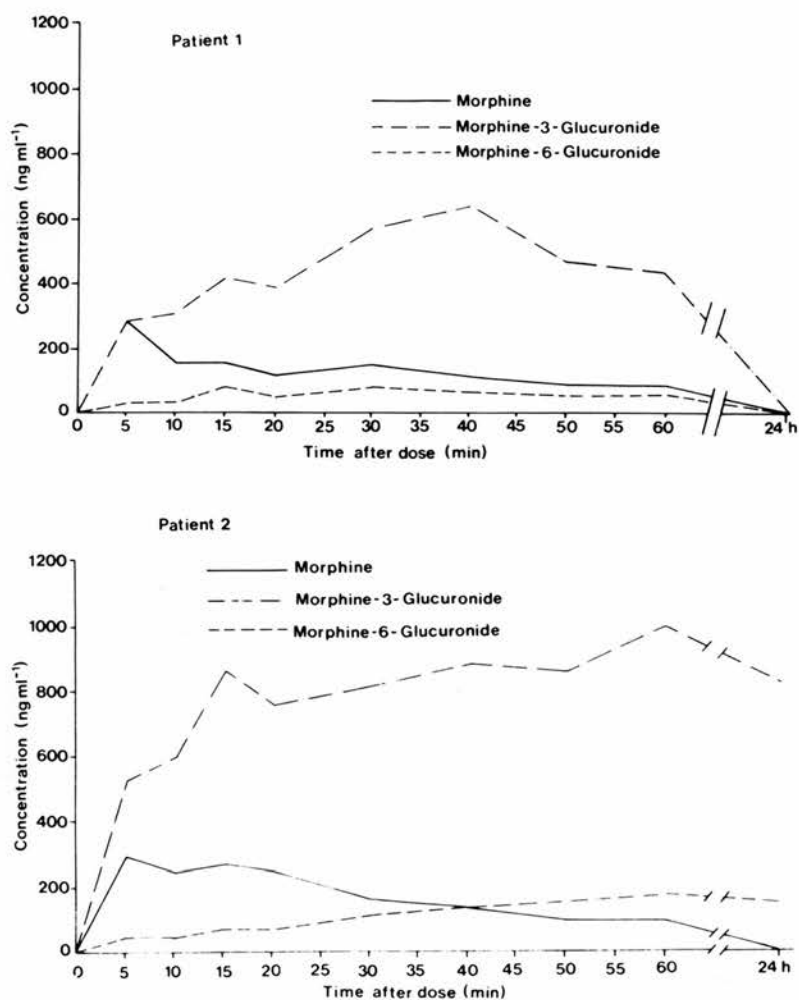


Figure 11.4: Plasma morphine, morphine-3-glucuronide and morphine-6- glucuronide concentrations in Patient 1 and Patient 2 for 60 minutes preoperatively and at 24 hours postoperatively.

The pharmacokinetic parameters of morphine in Patient 1 were; half life 0.47hr, volume of distribution at steady state 4.4 l/kg and clearance 93ml/min/kg, and in Patient 2 half life 0.52hr, volume of distribution at steady state 3.4 l/kg and clearance 68ml/min/kg.

The plasma concentration of M3G increased in both patients but more steeply and to higher values in Patient 2. While the concentration of M3G then decreased in Patient 1, it was maintained in Patient 2. Plasma M6G concentration rose to a peak at approximately 15 minutes in Patient 1 and was maintained at this level subsequently. In Patient 2, however, the concentration of M6G again increased gradually for the first 15 minutes but thereafter it continued to increase, and at the end of the hour the value was greater than that of the morphine base.

Patient 1, 24 hours after his original dose of morphine had no detectable morphine, M3G or M6G present in his plasma. Patient 2, 24 hours after her original dose of morphine, had no detectable morphine base but levels of M3G and M6G were unchanged from concentrations measured at 60 minutes.

Intraoperative details for both patients are shown in Table 11.4.

	Patient 1	Patient 2
Duration of Surgery(hours)	5	5.5
Blood loss (ml/kg)	79	80
Transfusion Requirement ml/kg	61	100
Urine output (ml/kg)	6.0	0

Table 11.4: operative details regarding the two paediatric patients undergoing liver transplantation.

The duration of surgery and the blood loss were comparable for both patients and both received a large blood transfusion. Patient 2, however, was anuric throughout the operation, whereas patient 1 had an adequate urine output. The patients' postoperative urine output, conscious level and opiate requirement are shown in Figure 11.5.

Patient 1 maintained a urine output of approximately 1ml/kg/hr. He required regular administration of fentanyl for analgesia, but in spite of this, remained difficult to sedate to allow satisfactory control of his ventilation and further morphine was required 26 hours after his initial dose. Patient 2 continued to have an inadequate urine output. In addition, although she received no further opiate, there was no response to painful stimuli and pinpoint pupils were observed throughout her oliguric period.

Both patients started to produce bile promptly postoperatively and continued to do so, indicating recovery of liver function.

Patient 2 eventually responded to diuretic therapy with a large diuresis. One hour after the start of her diuresis, she became responsive to stimuli and her pupils enlarged slightly. Six hours later she required further sedation.

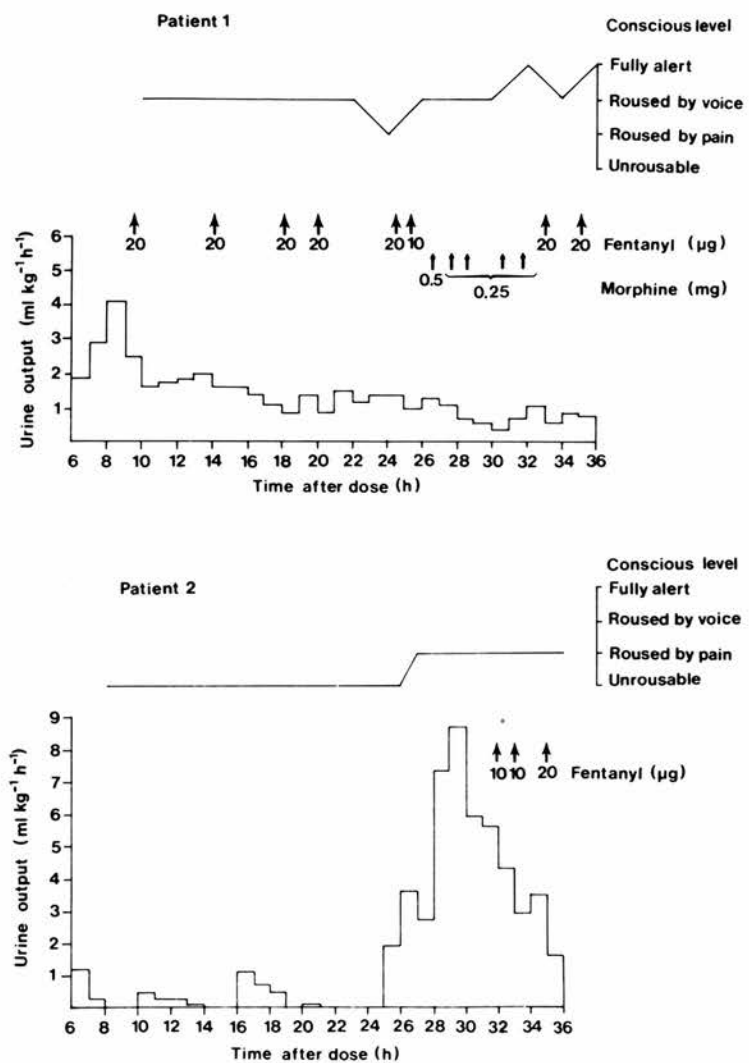


Figure 11.5: Postoperative urine output, conscious level and opiate requirement for Patient 1 and Patient 2.

Discussion

Both the patients described here had liver failure during the initial study period before surgery, yet both metabolised morphine rapidly; plasma morphine levels decreased and the concentrations of M3G and M6G increased. Neither patient was capable of producing bile at this time but plasma levels of morphine decreased nevertheless. No second peaks were observed which may refute the importance of the biliary excretion of morphine.

The clearance of morphine in these children was greater than that previously reported in paediatric patients (Dahlstrom et al 1979). This may reflect the different methods used to estimate plasma morphine concentrations or it may result from the relatively short sampling period available in our study, before surgery was undertaken, with its consequent haemodynamic instability.

The main differences between the two children were their renal function and plasma concentrations of M3G and M6G. Patient 1 had normal renal function and had eliminated all detectable morphine, M3G and M6G from his blood by 24 hours after administration of the initial dose. Patient 2 had impaired renal function and a poor urine output. Morphine base was no longer detectable at 24 hours after administration but high concentrations of

M3G and M6G were present in spite of a large intraoperative blood transfusion to replace an operative blood loss approximating to her circulating blood volume. This accumulation of morphine metabolites would appear to indicate that an adequate urine output is important for their elimination. The clinical evidence of recovery in Patient 2 when her diuresis started adds support to this hypothesis.

Morphine 3 glucuronide is thought to be inactive parenterally, but M6G is known to be a powerful analgesic (Shimomura et al 1971). Its other actions, however, are unknown. Patient 2 was unresponsive to pain and had pinpoint pupils in association with increased plasma concentrations of M6G and this may indicate other opiate-like properties, particularly sedation. The assay method used was calibrated for only M3G and M6G. Other metabolites (such as normorphine), possibly active, were not measured but may have been present.

The two patients described here illustrate that morphine can be rapidly metabolised, even in the presence of severe liver failure. Impairment of renal function with a low urine output in one of the patients was associated with accumulation of M3G and M6G and with prolonged narcosis. Morphine has active metabolic products and it may be these that produce the clinically observed prolonged action of morphine in patients with renal

failure. Two further patients are described to demonstrate the importance of renal function and the elimination of morphine and its metabolites.

Patient 1.

British Medical Journal (1984) 289; 1071-1072

This 30-year-old male patient received a morphine infusion for analgesia and sedation following liver transplantation. Postoperatively he developed renal failure which was managed by a regimen of continuous arterio-venous haemofiltration and intermittent haemodialysis. His conscious level deteriorated on the ninth day and morphine toxicity was suspected despite the presence of midsized pupils. During this period, he had received 225mg morphine sulphate. The administration of naloxone produced a prompt improvement, and samples were taken for subsequent plasma morphine assay by radioimmunoassay. The results are shown in Figure 11.6, together with his morphine dosage and the periods of haemodialysis and haemofiltration.

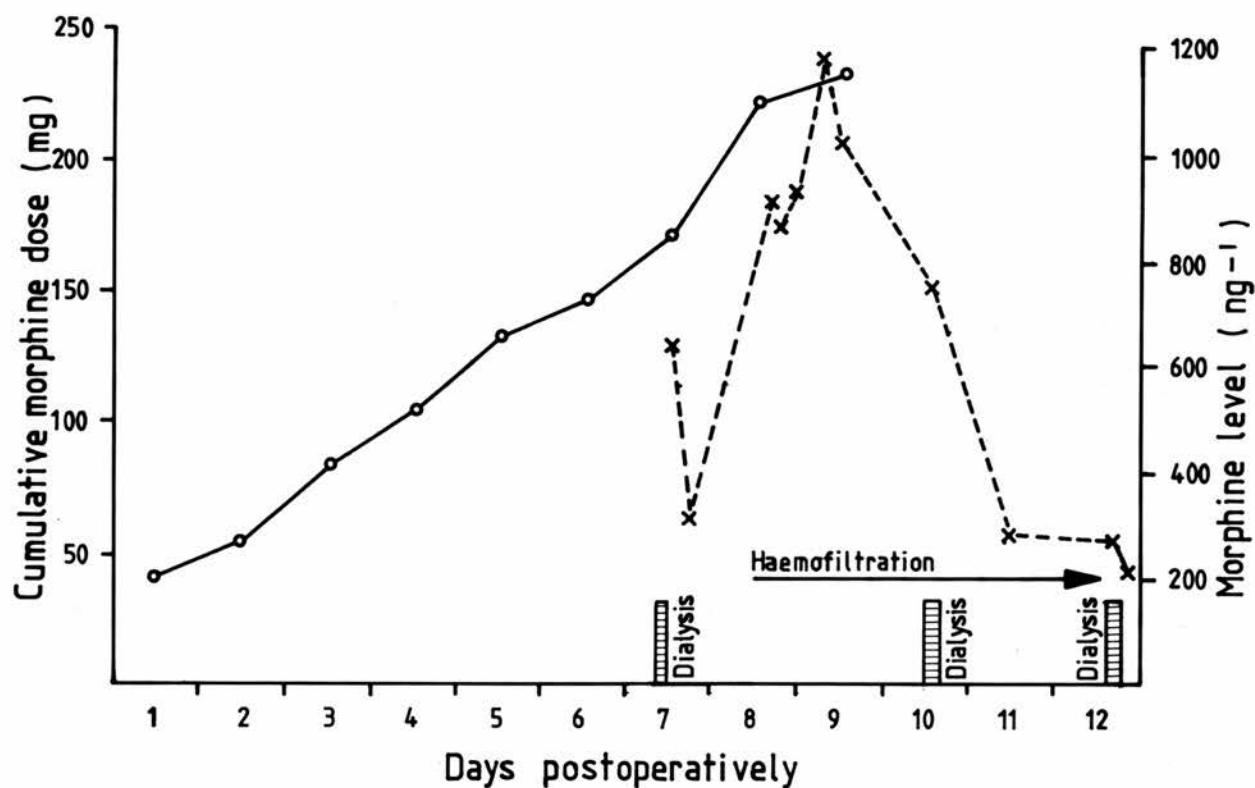


Figure 11.6: Cumulative morphine dose (O-O) and plasma morphine concentration (x-x) in a patient receiving an IV morphine infusion following liver transplantation.

Patient 2

Lancet (1985) 1: 1100

This patient, a 49-year-old woman with primary biliary cirrhosis, had participated in the initial (2.5mg) study of morphine pharmacokinetics following liver transplantation. Her postoperative course was complicated by renal failure due to sepsis and she required continuous arterio-venous haemofiltration.

Informed assent was obtained from her husband for a second study on the 30th day after the first. During the first investigation her renal function was normal (creatinine $<100 \mu\text{mol/l}$, urea $6.8 \mu\text{mol/l}$, urine output 2.6 l in this 24 hour period); on the second occasion her renal failure was controlled with continuous arterio-venous haemofiltration and dialysis (creatinine $390 \mu\text{mol/l}$, urea $73.4 \mu\text{mol/l}$, urine output 0.1 l in this 24 hour period). Thus, she was studied initially with normal renal function but poor hepatic function and subsequently with reasonable liver function but no renal function. Plasma concentrations of morphine measured during the two studies are shown on Figure 11.7. During the first study peak plasma morphine concentrations of 16.8 ng/ml were seen after 4 hours, following which morphine concentrations returned to baseline within 12 hours.

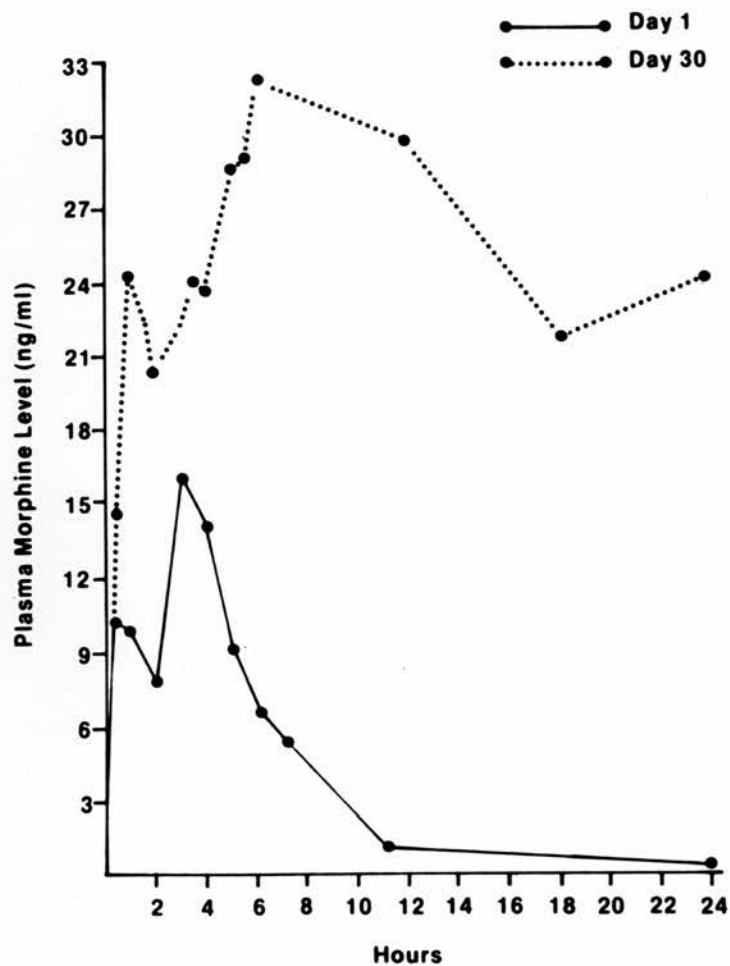


Figure 11.7: Plasma morphine levels for 24 hour period in a patient following liver transplantation. Day 1: immediate postoperative study. Day 30: patient in renal failure.

However, on the second occasion a peak plasma morphine concentration (C_{max}) of 32.2ng/ml occurred after 6 hours and the concentration did not decrease below 20ng/ml during the entire period of study.

The first study was performed when the patient had good renal function but impaired liver function following an ischaemic period of 297 minutes. The second was undertaken when she was in renal failure but her liver function, apart from an increased bilirubin, was essentially unchanged. Although the pattern of results was similar on both occasions, during the second study the peak plasma level was almost double that of the earlier study, with little elimination of the morphine during this period of study. The difference in C_{max} may represent a different volume of distribution, though the sustained high plasma concentrations of morphine on the second occasion cannot be explained in this way.

Discussion of the Two Patients

The first patient illustrates the problems of depressed conscious level which may occur when opiates are administered to patients with impaired renal function; the second patient offers some explanation of the mechanism behind these difficulties, since she was studied before and after she developed renal failure. As can be seen from the first patient, plasma concentrations of morphine decreased during periods of

haemodialysis but subsequently increased again due to redistribution from body compartments. During continuous arterio-venous haemofiltration, however, concentrations remain constant.

The high plasma concentrations of morphine obtained in both patients when in renal failure demonstrate the importance of the kidney in the elimination of morphine.

Increased clinical effects after morphine therapy in patients with renal failure have led some authors to suggest that the kidney may be important in morphine metabolism (McQuay and Moore 1984a,b; McQuay 1986). This appeared to be supported by pharmacokinetic studies that used nonspecific assays that did not differentiate between unchanged morphine and its metabolites (Moore et al 1984b). More recent work using HPLC (Aitkenhead et al 1984) and a specific radioimmunoassay (Chauvin et al 1987) has shown increased volumes of distribution and accumulation of metabolites, but no decrease in clearance of unchanged morphine in patients with end stage renal disease. Thus it is thought that the accumulation of these metabolites which are pharmacologically active is the cause for the apparent sensitivity of renal failure patients to morphine.

The analytical method used for these two patients employed the radioimmunoassay method described by Moore et al (1984a) which has difficulty in distinguishing

morphine from M6G. More recent studies in patients with renal failure, using high performance liquid chromatography (Aitkenhead et al 1984) and a specific radioimmunoassay (Chauvin et al 1987) to measure plasma morphine concentrations, showed a variable volume of distribution but a normal morphine clearance. This has led to speculation regarding the possible role of morphine metabolites. Morphine has a number of active metabolites, including M6G (Shimomura et al 1971) and normorphine (Lasagna and De Kornfield 1958; Johannesson and Milthers 1962); the 3-glucuronide is thought to be inactive when administered parenterally (Shimomura et al 1971; Sasajima 1970). Morphine-6-glucuronide administered parenterally to rats has an analgesic potency 4 times that of morphine and a duration of action twice that of morphine. Intracisternal administration of M6G reveals an analgesic potency 44 times that of morphine (Shimomura et al 1971).

Ball and her colleagues (1985) from Oxford studied morphine clearance in critically ill patients with varying degrees of renal dysfunction using their radioimmunoassay to measure morphine. They concluded that morphine clearance was dependent upon renal function. As already discussed, this radioimmunoassay method cross reacts with M3G to a small extent (5%), but with M6G to a much greater degree (150%), and they were measuring clearance of morphine and its metabolites.

Osbourne and his colleagues (1986) demonstrated increased plasma concentrations of M6G associated with intoxication after papaveretum administration in three critically ill patients. They attributed the coma to M6G, in a similar way to the child with renal failure discussed in an earlier part of this thesis. It is of note that all of Osbourne's patients developed renal failure after receiving papaveretum, which contains codeine, a substance implicated as a causative agent in renal failure (Shelly et al 1989).

In patients with renal failure, morphine is metabolised normally but the metabolites are not eliminated in oliguric or anuric states. This leads to accumulation of morphine metabolites and in particular of M6G, which results in the clinical signs of opioid intoxication.

To examine further the question of second peaks and the disposition of morphine the original study was continued using 10mg (rather than 2.5mg) of morphine sulphate and HPLC as the analytical method. I was assisted in this study with the sample collection by Dr Maire P Shelly and with the sample analysis by Mr K Quinn (Ph D student).

THE PHARMACOKINETICS OF MORPHINE IN PATIENTS

FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

British Journal of Anaesthesia (1989) 63; 375-379

Patients and Methods

Seven subjects were studied in a similar way to the first study in this chapter. After a 10 ml baseline arterial blood sample had been collected, morphine sulphate (10mg) diluted to 10ml with 0.9% saline was injected over a 2 minute period through a centrally placed venous catheter. The frequency of sampling was increased compared with the original study and blood collected at: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 12, 18 and 24 hours after drug administration. Urine and bile specimens were collected at: 1, 2, 3, 4, 5, 6, 12, 18 and 24 hours after drug administration. Blood samples were placed in a tube containing lithium heparin anticoagulant and mixed. The tubes were centrifuged at 3000rpm and the supernatant plasma removed and stored at -20°C in siliconised tubes prior to analysis.

Prior to and during the study period analgesia was provided with bolus doses of fentanyl, which does not crossreact with the assay method. Laboratory investigations, including liver function tests and creatinine clearance, were measured during the 24 hours of the study period. Additionally, during surgery

hepatic arterial blood flow following revascularisation of the donor liver was measured using a Stratham SP12 electromagnetic flowmeter.

In order to obtain the required degree of sensitivity and specificity, plasma and urine morphine were measured using the radioimmunoassay procedure which excludes metabolites from the measurement (Quinn et al 1988). Plasma and urine M3G and M6G concentrations were measured by HPLC (Svensson 1986).

The curve-fitting procedure gave calculations for the area under the plasma concentration versus time profile (AUC), distribution half life ($t_{1/2\alpha}$), elimination half life ($t_{1/2\beta}$), volume of distribution of the central compartment (V_1), apparent volume of distribution (V_d) and total body clearance of morphine normalised for body weight (Cl).

Results

Demographic details of the patients and their diagnoses are presented in Table 11.5. Postoperative liver function tests, creatinine clearance, ischaemic time and intraoperative hepatic arterial blood flow for each patient are shown in Table 11.6.

Patient	Sex	Age	Weight	Diagnosis
	(M/F)	(yrs)	(kgs)	
1	F	52	96.0	Hepatoma
2	M	36	71.8	Budd-Chiari Syndrome
3	M	35	41.0	Hepatoma
4	F	19	82.0	Budd-Chiari Syndrome
5	F	37	55.0	Wilson's Disease
6	F	26	50.8	Hepatocellular Carcinoma
7	F	44	37.0	Primary Biliary Cirrhosis

Table 11.5: Demographic details and presenting diagnosis of the seven patients studied.

Patient	Bilirubin	ALT	AP	Creatinine	Ischaemic Time		Intraoperative
	(μ mol/l)	(U/l)	(U/l)	Clearance	(mins)		HABF
				(mls/min)	Warm	Cold	(ml/min)
1	76	84	223	54.8	391	130	420
2	328	136	387	101	267	47	140
3	228	2120	385	63.3	284	71	60
4	37	412	181	88	259	42	400
5	40	181	301	63.7	254	59	1000
6	47	148	258	54.3	231	34	213
7	79	104	484	54.6	236	31	600

Table 11.6: Postoperative liver function tests, plasma creatinine and hepatic ischaemic times in seven patients.

No patient had major renal impairment during the period of study; the creatinine clearance in all cases was in excess of 50ml /minute (Sharpstone and Trafford 1984).

The plasma concentrations of morphine, M3G and M6G are shown in the Figure 11.8. Following the injection of morphine an exponential decline is observed with no detectable plasma morphine after 24 hours. Four hours after morphine administration (the peak concentration for M3G), levels of M3G exceeded the parent drug nearly ten-fold. No secondary peaks were seen in the plasma concentrations of morphine. Results of the pharmacokinetic analysis are summarised in Table 11.7.

Elimination of M3G, like M6G, appeared to be slow, with detectable levels of both metabolites at 24 hours. Because of this, it was not possible to derive any pharmacokinetic parameters for the elimination of the glucuronides since no further plasma samples were taken after 24 hours. Intraoperative hepatic arterial blood flow, which was very variable, did not appear to relate to the postoperative clearance. Recovery of morphine at the 1ng/ml level (the limit of detection) was 89%. Recovery from plasma and urine for both glucuronides was greater than 90%. The mean recovery of morphine, M3G and M6G from urine is presented in Figure 11.9.

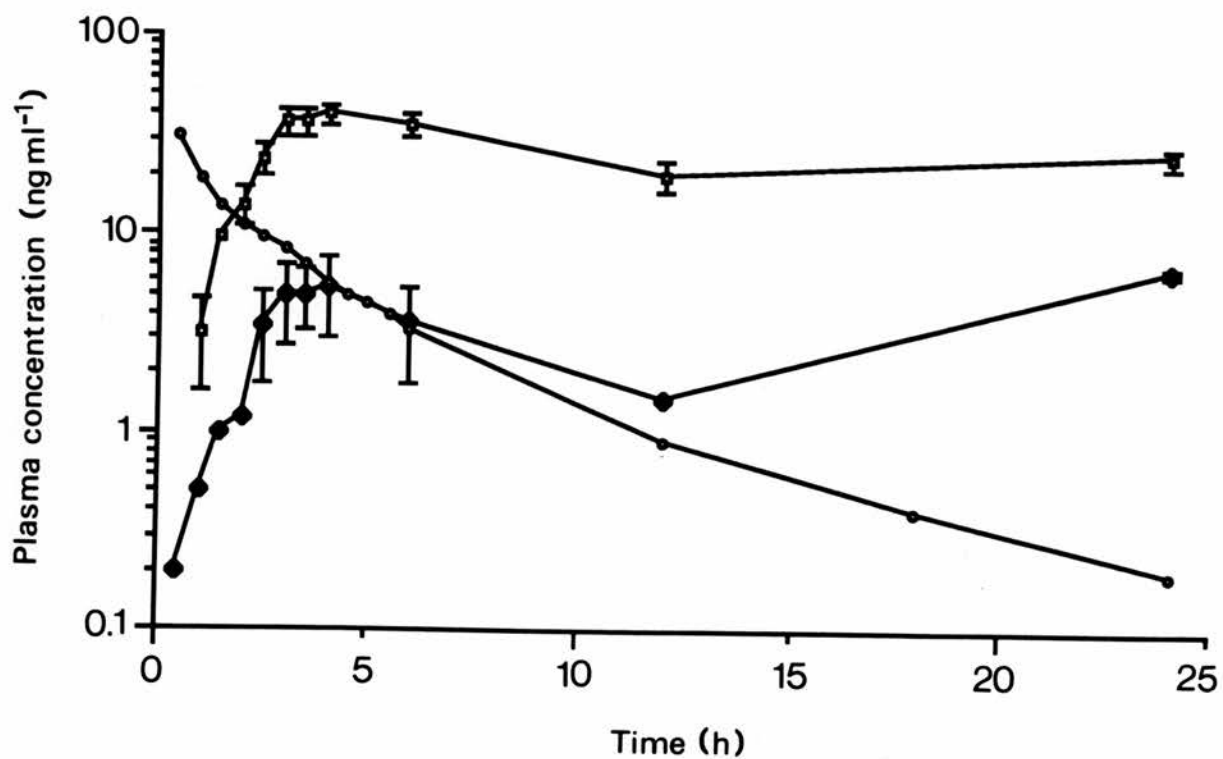


Figure 11.8: Plasma concentrations of morphine (○), M3G (□) and M6G (◆) following intravenous administration of 10mg morphine sulphate in patients following liver transplantation.

Patient	Body Weight (kg)	Age (yrs)	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (min)	V_1 (l/kg)	V_d (l/kg)	Cl (l/kg/min)	AUC (ng h/l)
1	96	52	28.5	252	1.53	3.78	0.62	125.8
2	71.8	36	31.3	198	1.94	4.8	1.09	103.9
3	41	35	15.0	130	3.26	10.7	3.44	53.4
4	82	19	27.4	231	1.49	3.9	0.70	130.3
5	55	37	43.3	320	3.27	14.3	1.86	73.7
6	50.8	26	15.5	212	1.26	7.0	1.38	107.5
7	37	44	20.1	175	2.51	10.3	2.46	82.7
Mean	61.9	36	26	217	2.2	7.8	1.65	96.8
SEM	8.3	4	4	23	0.3	1.5	0.4	10.6

Table 11.7: Pharmacokinetic parameters calculated after 10mg morphine sulphate administered iv in patients following orthotopic liver transplantation.

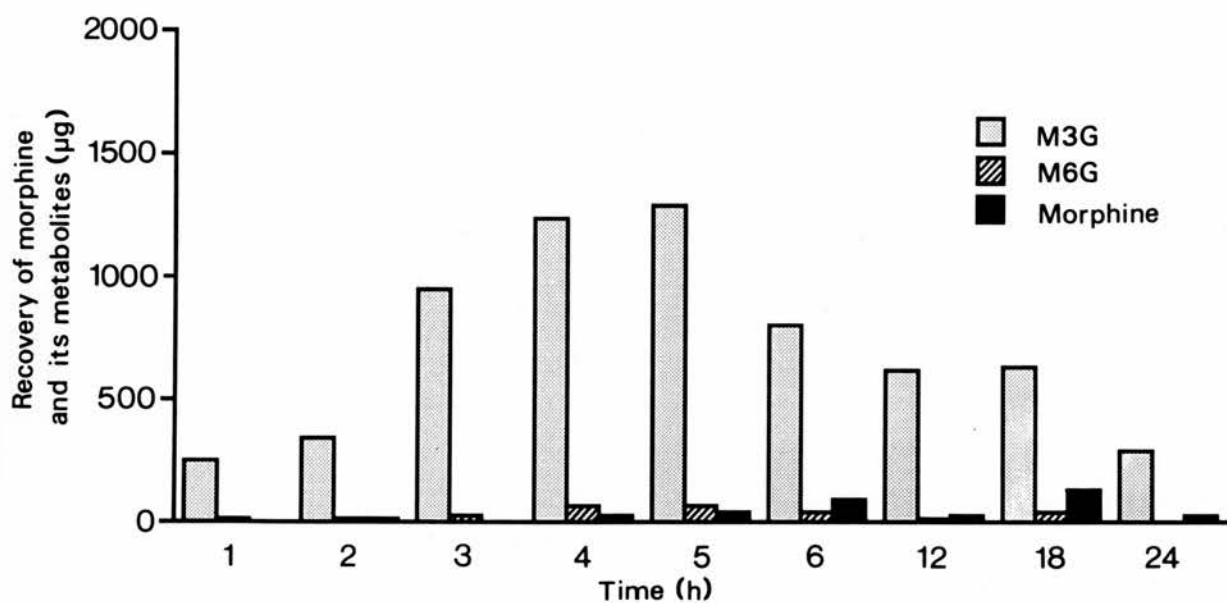


Figure 11.9: Mean urine recovery of morphine, M3G and M6G following intravenous administration of 10mg morphine sulphate in patients following liver transplantation.

Morphine was predominantly recovered as M3G (85%), with 3.6% as M6G and only 4.5% as the unchanged drug. The remainder of the morphine dose may be accounted for either in the systemic circulation or excreted in the bile. An attempt was made to analyse morphine, M3G and M6G in bile specimens but this did not prove sufficiently reliable, owing to coeluting compounds, for inclusion in the pharmacokinetic analysis.

Discussion

A biexponential decline in plasma morphine concentration was evident in each patient. A more rapid distribution phase has been observed in other studies but the first sampling point in our study was 30 minutes after drug administration and this phase was therefore not seen. The elimination half life was 2.4 hours; earlier workers using specific assays for morphine have found similar elimination half lives of about 2 hours (Berkowitz et al 1975; Stanski, Greenblatt and Lowenstein 1978; Dahlstrom et al 1979).

The plasma clearance of morphine [mean (SEM)] in this study, 1.65 (0.47) litre/kg, was higher than previous estimates in healthy volunteers and surgical patients (Goldberg 1970), and the recovery of morphine and its glucuronides from urine indicates that the excretion of morphine was virtually complete. In addition, the wide range of clearances found may be a reflection of the

interpatient variability in chronically-ill subjects with pre-existing liver disease. Clearance values greater than hepatic arterial blood flow were observed in four of the seven patients. However, the contribution of portal blood flow to the clearance was not assessed and probably explains this discrepancy. Alternatively some extrahepatic sites of morphine metabolism may exist.

Patients with chronic liver disease may have impaired renal function, although perioperative renal protection with low dose dopamine may improve this (Chapter 15). Additionally, the periods of stress, surgical trauma and drug therapy may induce a period of oliguria when renal elimination of drug metabolites is impaired (Bion et al 1986). The patients in this study had adequate renal function during the period of investigation, as indicated by a creatinine clearance in excess of 50ml /minute. Although the elimination half life would appear to coincide with documented values, the estimates for volume of distribution and clearance differ. Hepatic arterial blood flow was greater than expected, but since this was measured intraoperatively the importance of the measured value to a study performed in the following 24 hours requires careful interpretation. The influence of direct surgical trauma in the denervated hepatic artery with concurrent dopaminergic stimulation is unknown.

The disposition of morphine in patients with liver disease has received limited study. The combination of age, disease, anaesthesia and surgery may have contributed to the observed values found for the volume of distribution and clearance, and may explain the discrepancy with other pharmacokinetic studies. In this group of patients the metabolism of morphine was found to be almost complete, with only 4.5% of unchanged morphine recovered in urine after 24 hours. Total clearance was found to be greater than liver blood flow, indicating the possibility of extrahepatic metabolism.

Since no second peaks were seen during this study, those seen during the first study described in this chapter probably represented cross-reactivity between morphine, M3G and M6G. The radioimmunoassay used was known to cross react with M3G to some extent but was unable to distinguish morphine from M6G (Aherne 1982). Further support for this hypothesis is gained by studying the individual peak values in the study. In some patients the second peak has a greater value than the first peak. M6G is now known to have an affinity of approximately 150% (Morphine = 100%) for the antibody and the appearance of this metabolite at this time would explain the phenomenon.

SITE OF MORPHINE METABOLISM

Historically the liver has always been considered the major organ of morphine metabolism. This was contested by a study suggesting normal pharmacokinetics in patients with cirrhosis (Patwardhan et al 1981). However, a more recent study has shown a decrease in the clearance of morphine (Mazoit et al 1987) in cirrhotic patients. The differences between these studies may be related to the severity of the liver disease in the patients studied, but comparisons between patients are made difficult as conventional tests of liver function are poor predictors of changes in the pharmacokinetics of drugs (Secor and Schenker 1987). The metabolism of other drugs which undergo glucuronidation shows that glucuronidation (Kraus, Desmond and Marshall 1978) may be relatively spared compared with other metabolising functions, like oxidation, in severe liver disease. An alternative explanation is that the enzyme system UDP glucuronyl transferase is found in other extrahepatic sites such as the gut or kidney, and that these may be significant sites for metabolism in man. The primary site of metabolism after therapeutic doses has been debated. Clinical and laboratory studies have suggested two significant sites for morphine metabolism, the liver and the kidneys. In vitro studies of isolated kidney and liver have shown the presence of uridinediphosphoglucuronyltransferase (UDP glucuronyl transferase)

(Pacifi and Rane 1982; Pacifi et al 1982) although these do not necessarily relate to function in vivo. Renal metabolism of morphine has been postulated (McQuay and Moore 1984a,b; Moore et al 1984b; Ball et al 1985) based on observations in patients with renal failure.

To resolve the speculation about the importance of the liver in the metabolism of morphine, the pharmacokinetics of morphine were studied during the anhepatic phase of liver transplantation. I was assisted with the sample collection by Dr A Bodenham (Registrar) and Mr K Quinn (Ph D student).

EXTRA-HEPATIC METABOLISM OF MORPHINE DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION

British Journal of Anaesthesia (1989) 63; 380-384

Patients and Methods

Seven adult patients who were likely to run an uncomplicated intraoperative course were studied. Apart from the patients with small intrahepatic tumours, most patients undergoing liver transplantation have advanced liver disease with associated portosystemic shunts and coagulation problems. Surgery may be technically difficult with large blood losses which would give rise to difficulties in performing this study. The patients in this series were chosen as having a low risk of this complication, i.e. those with good

coagulation, lack of concurrent medical problems and no previous intra-abdominal surgery.

Anaesthesia was conducted as previously described using an oral benzodiazepine for premedication. Analgesia was provided by intermittent bolus injections of fentanyl.

Baseline blood and urine samples were taken immediately before the anhepatic phase. Three minutes after the anhepatic phase had started 10mg of morphine, diluted in 10ml of saline, was administered into a central vein. Blood samples were collected at 2, 5, 10, 15, 20, 30, 40 minutes after the injection and immediately before reperfusion. Although the perfusion of the kidneys and intestines is compromised during the anhepatic phase these patients usually produce 50-100ml of urine during this period and samples were therefore collected at 5 and 30 minutes and immediately before reperfusion.

On reperfusion the sampling protocol was repeated with blood and urine samples taken at the same times as during the anhepatic phase. Blood loss and replacement, urine output and body temperature were recorded for each stage. Blood samples were placed in lithium heparin tubes, centrifuged at 3000 rpm for 5 minutes, and then separated into plain, glass siliconised tubes with screw caps to minimise adsorption. Urine and plasma samples were stored at -20°C for later analysis by HPLC.

Results

The details of the seven patients studied are shown in Table 11.8. All patients had significant hepatic dysfunction except for patient 2 who had a solitary hepatoma.

Table 11.9 lists some of the operative details of these patients. The blood losses, although large by general surgical standards, are not unusual for an uncomplicated liver transplant operation. All patients produced urine during the anhepatic period. The cold ischaemic times of 406 (138) minutes were also typical.

Results of assays for morphine and its metabolites in plasma and urine are shown in Figure 11.10 and Table 11.10. Plasma concentrations of morphine decreased during the anhepatic period, consistent with the distribution phase after injection, followed thereafter by little change. During the anhepatic phase, M3G was detectable in low concentrations in plasma (less than 7ng/ml) and urinary concentrations increased to a maximum of 137ng/ml during the anhepatic phase. Morphine-6-glucuronide was detected at a maximum of 1.4ng/ml in plasma and 22.3ng/ml in urine during this phase. Normorphine was undetectable in both plasma and urine throughout the study period.

Patient	Age (Yr)	Sex	Weight (Kg)	Presenting diagnosis
1	52	male	56	Primary biliary cirrhosis + hepatoma.
2	41	male	70	Carcinoma of liver.
3	35	male	77	Sclerosing cholangitis + cholangiocarcinoma.
4	51	female	60	Primary biliary cirrhosis.
5	29	female	60	Alcoholic cirrhosis.
6	42	female	54	Chronic active hepatitis.
7	52	male	60	Alcoholic cirrhosis + hepatoma.

Table 11.8: Demographic data and presenting diagnosis of the seven patients.

Phase	Blood loss (mls)	Duration (mins)	Urine volume (mls)
Dissection	1788 (1147)	135 (45)	345 (279)
Anhepatic	1657 (1029)	56 (9.4)	57 (47)
Reperfusion	2862 (2288)	95.7 (19.5)	282 (182)

Table 11.9: Operative details [mean (SEM)] of the seven patients.

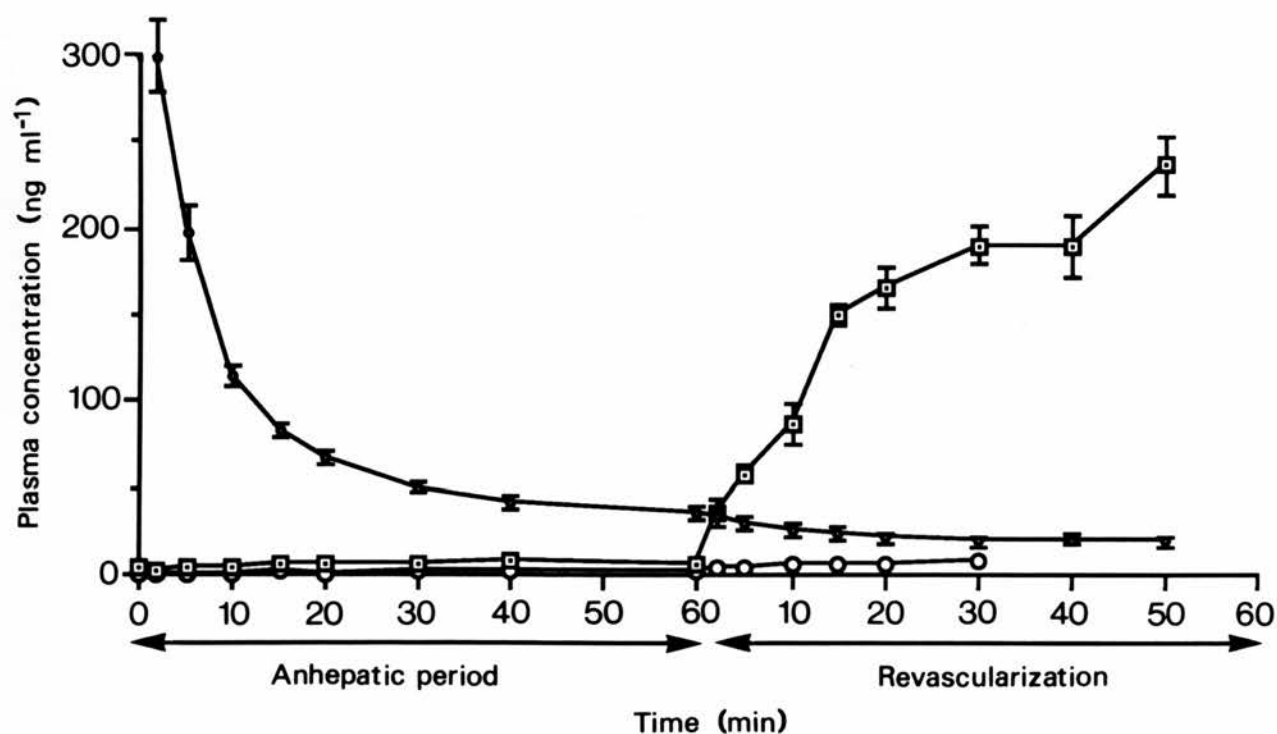


Figure 11.10: Plasma concentrations of morphine (●), M3G (□) and M6G (○) during the anhepatic and reperfusion phases of orthotopic liver transplantation.

	Morphine	M3G	M6G
	ng/ml	ng/ml	ng/ml
Baseline	0	0	0
Anhepatic Phase			
5 min	0	4.1 (2.1)	8.8 (4)
30 min	315 (105)	31 (15)	5.8 (3.2)
60 min	2167 (424)	137 (39)	22 (6)
Reperfusion Phase			
30 min	1402 (305)	66 (24)	13 (7)
60 min	812 (307)	132 (44)	11 (6)

Table 11.10: Urinary concentrations [mean (SEM)] of morphine, morphine-3-glucuronide and morphine-6-glucuronide during the anhepatic and reperfusion phases of liver transplantation in seven patients.

Mean concentrations of both plasma and urinary M3G increased rapidly on reperfusion of the transplanted liver to a maximum of 236ng/ml and 132 ng/ml respectively. Plasma concentrations of M6G increased to a maximum of 7.1ng/ml and decreased slightly in urine to 11.4ng/ml during this period of study.

Discussion

Hug and his colleagues (1979) measured morphine metabolism during the anhepatic phase of liver transplantation in man but could not measure the metabolites directly. They similarly found insignificant metabolism during this period. In contrast, studies in the functionally anhepatic dog showed that morphine was glucuronidated to approximately equal extents by hepatic and extrahepatic tissues (Jacqz et al 1986). The lung is known to metabolise and take up certain endogenous and exogenous substances (Bakle 1982). Studies in anaesthetised and postoperative patients showed significant uptake but no metabolism of morphine (Persson et al 1986; Roerig et al 1987). Although not metabolically active, the lung is thought to act as a reservoir for morphine and other basic drugs between the right and left circulations, although this remains to be proved in humans (Chapter 10).

The appearance of morphine metabolites in the urine during the anhepatic period, despite the plasma

concentrations being undetectable, may be explained in two ways. The kidney may be concentrating small quantities of morphine metabolites in the plasma which are undetectable by the HPLC. Alternatively, the kidney could be an extrahepatic site for morphine metabolism, although if it were significant larger concentrations of metabolites would be expected in the urine.

The lack of significant metabolism of morphine in our patients during the anhepatic period of liver transplantation suggests that, in the group of patients studied, the liver is the predominant organ of morphine metabolism. It is also clear that the transplanted liver begins to metabolise rapidly morphine shortly after reperfusion.

CHAPTER 12

ANALGESIA: THE NEW OPIOIDS

The increasing recognition of the problems associated with the established narcotics, particularly long and unpredictable duration of action and respiratory depression, led to the development of new agents. The characteristics of two of these agents, alfentanil, with its short duration of action, and nalbuphine, a mixed agonist-antagonist with a ceiling effect on respiratory depression, might make them useful analgesics in patients after liver transplantation.

ALFENTANIL

Alfentanil is a potent opioid analgesic with a rapid onset and short duration of action. It has a small volume of distribution (0.45 l/kg) and a short elimination half life of 98 minutes in the healthy subject (Bower and Hull 1982). In common with other opiates, alfentanil produces respiratory depression, which has been shown to be comparable with fentanyl (Andrews et al 1983), although recovery is predictably faster. The cardiovascular effects of alfentanil have also been compared with fentanyl in anaesthetised patients (Rucquoi and Camu 1983). Both drugs showed no profound cardiovascular depression and improved

myocardial oxygen demand. These effects lasted for a shorter period with a bolus dose of alfentanil than with fentanyl. Alfentanil is widely used as an analgesic during anaesthesia and by infusion in artificially ventilated patients. The advantage of a short acting agent, given by continuous intravenous infusion, would be the ability to provide intense analgesia but still be able rapidly to terminate its effects, especially respiratory depression, when the infusion is discontinued.

Metabolism and excretion

Alfentanil is eliminated almost completely by hepatic biotransformation, only 0.4% of the dose being excreted in the urine as unchanged drug (Schuttler and Stoeckel 1982). The main metabolic pathways are oxidative N and O-dealkylation (Meuldermans et al 1988). No active metabolites have been found.

The estimated hepatic extraction ratio suggests that the total body clearance of alfentanil could be influenced by both changes in hepatic blood flow and intrinsic clearance (Reitz 1986). In contrast to fentanyl, the duration of effect of a single dose of alfentanil is more dependent on its total body clearance than on redistribution to tissues.

A decreased clearance has been demonstrated in patients

with cirrhosis (Ferrier et al 1985) but this is unchanged in patients with renal failure (Van Peer et al 1986). Its use, by continuous intravenous infusion, to provide sedation and analgesia to patients requiring intensive care has been investigated by several groups. A wide variability in clearance of the drug and the response of patients was shown in two of these studies (Yate et al 1986; Sear, Fisher and Summerfield 1987). Alfentanil is bound in plasma to α_1 -acid glycoprotein (AAG), an acute phase protein which increases in concentration following injury and stress including cardiopulmonary bypass (Hug et al 1983) and after liver transplantation (Chapter 6).

A study of the pharmacokinetics of alfentanil on two occasions in the first 24 hours after liver transplantation was performed to assess the importance of the various factors influencing its pharmacokinetics. In addition, this study evaluated whether changes in alfentanil pharmacokinetics (a drug clinically useful unlike test substances such as antipyrine) could be used to assess changing liver function after hepatic transplantation; recovery of liver function being associated with more rapid elimination whereas deterioration would result in slower elimination. This study was performed at the same time as the one entitled "Serum Acute Phase Proteins After

Orthotopic Liver Transplantation" described in Chapter 6. I was assisted with the sample collection by Dr Maire P Shelly and sample analysis by Dr Sue Walker (Department of Clinical Biochemistry).

THE PHARMACOKINETICS OF ALFENTANIL IN PATIENTS

FOLLOWING LIVER TRANSPLANTATION

In: J Cros, J-C1 Meunier, M Hamon (eds). Progress in Opioid Research, Advances in the Biosciences. Oxford: Pergamon Press, (1989) 75: 643-646

Patients and Methods

Seven consecutive patients were studied within three hours of return to the Intensive Care Unit after liver transplantation. At this time a baseline blood sample was collected and alfentanil, 20 $\mu\text{g/kg}$ diluted to 10 ml in 0.9% saline, was administered as a bolus over 1 minute through a centrally placed venous cannula. Samples of arterial blood were removed at 2, 5, 10, 20, 30, 60, 90, 120, 180, 360, 480, 600 and 720 minutes. At the end of this period, a further 20 $\mu\text{g/kg}$ of alfentanil was administered in a similar manner and an identical sampling protocol followed. Blood was collected into lithium heparin tubes, centrifuged and the supernatant plasma separated and stored at -20°C . Subsequent analysis was performed using a radioimmunoassay technique (Michiels et al 1983). Elimination half life, plasma clearance and

apparent volume of distribution were calculated using standard methods (Gibaldi and Perrier 1982).

Results

The preoperative diagnosis and details of the patients are shown in Table 12.1. In all patients pre- and postoperative liver function tests were abnormal (Table 12.2). Of particular note is the correction of low plasma concentrations of albumin in some patients to almost normal values postoperatively.

There was considerable variation in the pharmacokinetic parameters of alfentanil between the patients; this is quantified in Table 12.3 for individual patients during both study periods. Only one patient had essentially normal pharmacokinetic values throughout the study period. Four patients had an increased volume of distribution during the first study which decreased during the second study period. Two patients demonstrated a considerably reduced clearance of alfentanil.

Throughout the study period α_1 -acid glycoprotein levels increased to just above the normal range and these results, and the changes observed in liver function tests, are presented in Chapter 6. No relationship between changes in the liver function tests and alterations in the pharmacokinetics of alfentanil could be found.

Age	37.9 (3.21) years
Weight	61.7 (3.38) kg
Sex	3 male/4 female.
Cold ischaemic period	210-389 min
Anhepatic duration	59.4 (8.61) min
Diagnosis	Sclerosing cholangitis 3
	Chronic Active Hepatitis 3
	Polycystic liver 1

Table 12.1: Details of the patients studied following liver transplantation. Figures shown as mean (SEM), with range for duration of cold ischaemia.

Patient	Albumin (g/l)	Total Bilirubin (μ mol/l)	Alkaline Phosphatase (U/l)	Alanine Amino- transferase (U/l)
1 a	29	268	2810	444
b	29	*	*	*
2 a	27	284	115	25
b	29	103	32	84
3 a	14	332	228	86
b	29	226	111	1144
4 a	37	336	163	60
b	32	154	207	233
5 a	26	155	752	67
b	30	41	36	536
6 a	10	195	493	50
b	32	140	364	922
7 a	32	22	904	14
b	31	27	53	57

Table 12.2: Liver function tests (a) before and (b) immediately after liver transplantation. * = no result available.

Patient	$t_{1/2\beta}$ (min)		Clearance (ml/min/kg)		Vd (ml/kg)	
	1	11	1	11	1	11
1	730	330	0.425	0.956	447	455
2	158	66	6.220	3.620	1413	345
3	120	217	8.710	2.210	1502	689
4	82	67	6.630	5.070	780	492
5	267	231	4.110	3.840	1581	1279
6	365	385	0.833	0.807	438	448
7	257	347	3.470	1.930	1284	965
Normal Values	90		6.4		860	

Table 12.3: Elimination half life, clearance and volume of distribution of alfentanil in patients following liver transplantation. 1 = first study period, 11 = second study period.

Discussion

Alfentanil elimination is dependent upon hepatic clearance and this is decreased in patients with cirrhosis (Ferrier et al 1985). In this study, all the patients had abnormal liver function tests and the clearance of alfentanil varied considerably. The most marked change in pharmacokinetic parameters was seen in the volume of distribution, which decreased in four patients during the study period, in one subject (patient 2) to a quarter of its starting value. Alfentanil is significantly bound to AAG, which increases in concentration with acute stress. Large changes in the concentration of AAG might be expected to alter the volume of distribution of alfentanil. In this study, plasma concentrations of AAG were slightly increased above the normal range, but they did not increase sufficiently to explain the large decreases in the volume of distribution. This change may be a reflection of recovery from anaesthesia and surgery as well as diminishing fluid losses and shifts. Unfortunately, too few other studies of this drug report concentrations of AAG to enable comparisons to be made.

In addition to the changes in volume of distribution, all four of these patients had a reduced plasma clearance of alfentanil during the second study period. A considerably reduced clearance of alfentanil was seen in two other patients. A reduced

clearance has also been seen in patients with cirrhosis (Ferrier et al 1985), the elderly (Helmerts et al 1982) and the critically ill (Yate et al 1986; Sear et al 1987). A subset of the normal population are poor oxidizers of certain drugs, for example sparteine, phenacetin and debrisoquine, because they possess an abnormal cytochrome P 450 isoenzyme (Sloan et al 1978). It has been suggested that this group (about 3-10% of the Caucasian population) are extremely slow metabolisers of alfentanil (McDonnell et al 1982; McDonnell, Bartkowski and Kahn 1984). Other studies have shown that the reduced clearance demonstrated by these authors is not due to debrisoquine polymorphism (Meuldermans et al 1988; Lavrijsen et al 1988; Henthorn Avram and Krecie 1989)

No correlation could be found between changes in alfentanil pharmacokinetics and alterations in liver function tests. There are several influences that will change the pharmacokinetic variables for alfentanil in addition to liver function. Losses and alterations of body fluids and recovery from the combined effects of surgery and anaesthesia (including changes in hepatic blood flow) are the most significant. These changes probably affect other drugs in a similar way but have not been previously recognised.

The pharmacokinetic alterations observed in this study

appear to be unpredictable and may result in unwanted narcosis and respiratory depression. Alfentanil should therefore be used with care in patients after liver transplantation since a prolonged effect is possible. Owing to the large number of factors that affect the elimination of alfentanil, measures of this are unreliable indicators of liver function.

NALBUPHINE

Nalbuphine is a semisynthetic opioid agonist-antagonist of the phenanthrene series and is structurally related both to the potent narcotic analgesic oxymorphone, and to the narcotic antagonist naloxone. It provides analgesia comparable with morphine when used to relieve moderate to severe pain (Bahar, Rosen and Vickers 1985; Beaver and Feise 1978) and has been used for premedication (Chestnutt, Clarke and Dundee 1987), to reverse opioid induced respiratory depression (Moldenhauer et al 1985) and as an adjunct in balanced anaesthesia (Fahmy 1980; Fahmy, Sunder and Roberts 1982). Other properties of the drug include a low abuse potential (Ciarmelli 1984), haemodynamic stability (Lake et al 1982a) and a ceiling to ventilatory depression (Gal, DiFazio and Moscicki 1982), properties which may be considered advantageous in an analgesic used after liver transplantation. The

pharmacokinetic data available for nalbuphine are at present limited to healthy individuals and none is available for patients with liver disease. The purpose of this study was to investigate the disposition and elimination of nalbuphine in the period immediately following orthotopic liver transplantation. I was assisted with the sample collection by Dr A R Manara (Registrar); DuPont Pharmaceuticals Ltd arranged the assay of the samples by the Department of Anaesthesia at the University of Leicester.

THE DISPOSITION OF INTRAVENOUS NALBUPHINE FOLLOWING

ORTHOTOPIC LIVER TRANSPLANTATION

British Journal of Anaesthesia
In Press (Subject to Modification)

Patients and Methods

Twelve patients participated in this study of nalbuphine pharmacokinetics following liver transplantation immediately after arrival in the Intensive Care Unit.

A baseline sample of blood was collected, as were bile, urine and nasogastric aspirate samples, when available. Once haemodynamic stability was achieved, 0.15 mg/kg of nalbuphine hydrochloride, diluted to 10 ml in 0.9% sodium chloride, was administered over a fixed time interval of 1 minute via a central venous catheter and flushed in with a further 10 ml of 0.9% saline. Blood samples were collected from the indwelling radial artery cannula at 2, 5, 10, 15, 30, 45 and 60 minutes after the

nalbuphine was administered and at half-hourly intervals until six hours had elapsed. Further samples were collected at 12, 18 and 24 hours. Nasogastric, bile and urine samples were collected at hourly intervals for 6 hours and at 12, 18 and 24 hours after the administration of nalbuphine. The nasogastric samples were taken by aspirating the nasogastric tube, whereas bile was collected from the bile bag attached to the T-tube. The T-tube itself was not aspirated to avoid the danger of introducing infection into the biliary tree. No further nalbuphine was administered to the patients for the duration of the study. Additional analgesia was provided as required, initially using intermittent, intravenous bolus doses of fentanyl or morphine sulphate and later using bilateral intercostal nerve blocks with bupivacaine.

The blood samples were collected in glass lithium heparin tubes, centrifuged at 3000 rpm for 15 minutes, and the supernatant plasma separated and stored in plain glass tubes at -20°C until analysed. Bile, urine and nasogastric samples were collected in plain glass tubes and stored immediately at -20°C until analysis. Samples were analysed, in duplicate, by high pressure liquid chromatography with electrochemical detection using naltrexone as the internal standard (Aitkenhead, Lin and Achola 1988). The limit of sensitivity of the assay was $<1\text{ ng/ml}$ and the coefficient of variation was less than

5% throughout the range 1-1000 ng/ml. Spiked blank plasma showed no chromatograms of fentanyl, morphine, midazolam or bupivacaine at the elution times for nalbuphine or naltrexone.

Plasma concentration-time profiles were analysed by nonlinear regression analysis to determine the elimination rate constant. The AUC and its first moment, the AUMC between 0 and the final sampling point "t", were determined by the linear trapezoidal rule; the additional areas $AUC_{t-\infty}$ and $AUMC_{t-\infty}$ were calculated by routine formulae. Clearance was calculated as $dose/AUC_{0-\infty}$ and V_{ss} (apparent volume of distribution at steady state) and MRT (mean residence time) by model independent noncompartmental methods.

The renal clearance (ml/min) of unchanged nalbuphine was calculated as: $\mu g \text{ excreted in 24 hours} / AUC_{0-24h}$.

Results

Patient details are shown in Table 12.4. Plasma creatinine was normal preoperatively and remained so in all patients postoperatively. No haemodynamic instability was seen following the administration of nalbuphine. Blood loss was minimal in all patients during the study period. Postoperative liver function tests, obtained during the period of study, are shown in table 12.5.

Patient	Sex	Age	Weight	Diagnosis
	(M/F)	(years)	(kg)	
1	F	39	53.8	PBC
2	F	53	48	PBC
3	F	46	61	PBC
4	F	32	37	PBC
5	M	58	80	Hepatoma, cirrhosis
6	F	38	65	CAH
7	F	53	40	Chronic rejection
8	F	52	41.5	PBC
9	F	22	69.4	CAH
10	M	39	67	Haemangioendothelioma
11	F	46	65.8	PBC
12	F	49	63	PBC

Table 12.4: Patient information. PBC = Primary biliary cirrhosis; CAH = chronic active hepatitis; SC = sclerosing cholangitis.

Patient	Bilirubin $\mu\text{mol/l}$	Alkaline Phosphatase (U/L)	Albumin (g/l)	ALT (U/L)	PT (sec)
1	91	636	28	1692	19/15
2	444	1940	26	128	15/14
3	228	441	29	398	19/16
4	391	271	26	524	21/16
5	29	94	35	293	18/15
6	43	84	30	526	18/14
7	192	610	25	522	15/13
8	233	454	36	1530	17/15
9	244	108	28	575	25/16
10	69	132	23	868	18/15
11	102	110	20	590	20/15
12	150	48	34	776	26/17

Table 12.5: Liver function tests in the immediate postoperative period.

The mean plasma concentration/time curve for nalbuphine is shown in Figure 12.1. The mean (SD) elimination half life was 230 (144) min, mean residence time 278 (185) min, plasma clearance 17.5 (8.7) ml/kg/min and volume of distribution at steady state 3.91 (2.08) l/kg (Table 12.6).

Samples of bile and nasogastric fluid were not available at sufficiently regular intervals in each patient to allow any further analysis or conclusions to be drawn, but the mean concentrations that were obtained are illustrated in Figure 12.2.

The total amount of nalbuphine excreted in the urine ranged from 16.2-378.6 μg (mean 164.01). This represents 0.17-6.82% (mean 2.14%) of the total dose administered, and 85.5-100% (mean 96.5%) of this had been excreted within 12 hours of the administration of nalbuphine (Figure 12.3). The mean renal clearance was 0.30 ml/kg/min (range 0.04-0.61).

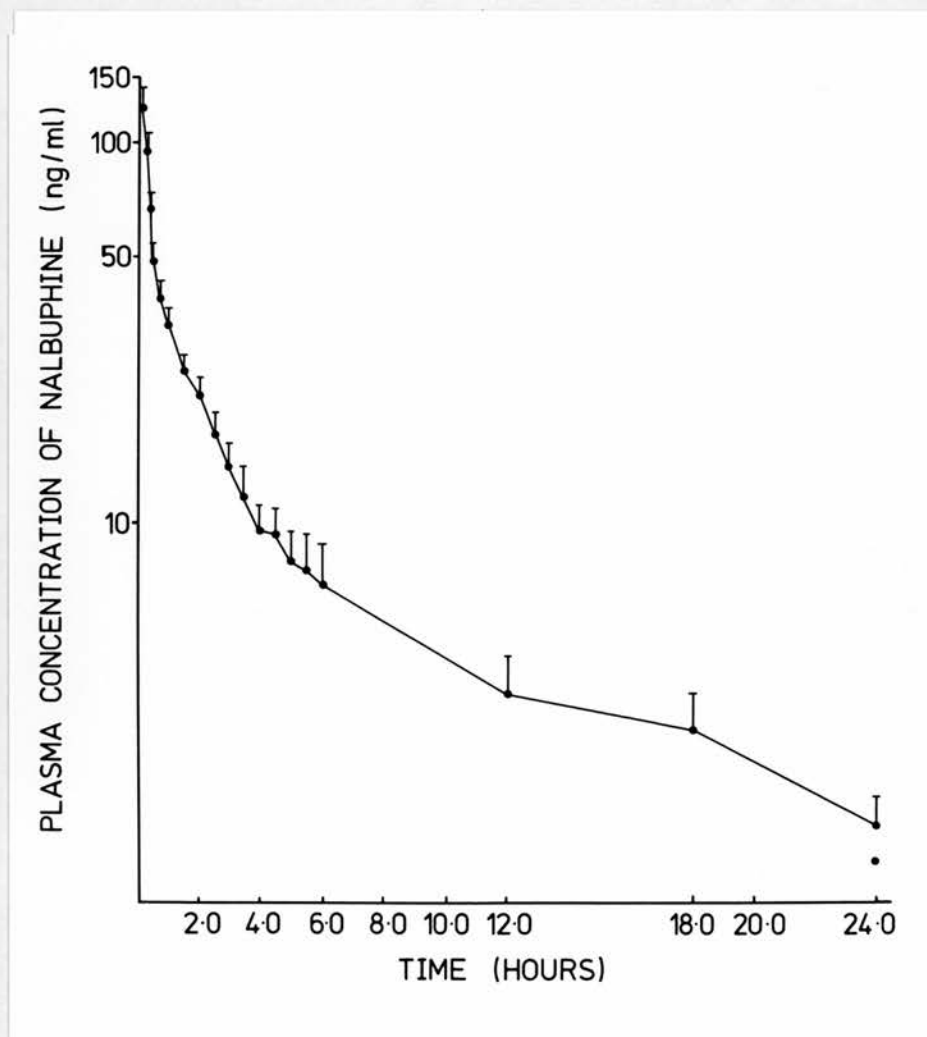


Figure 12.1: Mean (SEM) plasma concentration of nalbuphine against time after the IV administration of 0.15 mg/kg following orthotopic liver transplantation.

Patient	$t_{\frac{1}{2}\beta}$ (min)	MRT (min)	Vss (l/kg)	Cl (ml/kg/min)
1	97.6	114.0	1.70	14.9
2	322.2	415.6	3.21	7.7
3	141.4	165.6	2.85	17.2
4	309.1	384.6	3.41	8.9
5	206.6	216.1	3.07	14.2
6	282.9	277.1	5.96	21.5
7	101.6	119.6	4.30	36.0
8	413.3	510.0	9.00	17.7
9	102.6	143.0	3.83	26.8
10	493.3	636.9	4.13	6.5
11	59.5	74.7	1.55	20.7
Mean	230	278	3.91	17.5
SD	144	185	2.08	8.7
Volun-				
teers	222	-	315*	1.5**
Patients	135.5	150	156*	1.1**

Table 12.6: Pharmacokinetic parameters in 11 patients after the IV administration of 0.15 mg/kg nalbuphine following orthotopic liver transplantation. Normal values for volunteers (Aitkenhead, Lin and Achola 1988) and anaesthetised patients (Sear, Keegan and Kay (1987); note the different units * = l, ** = l/min used by these authors.

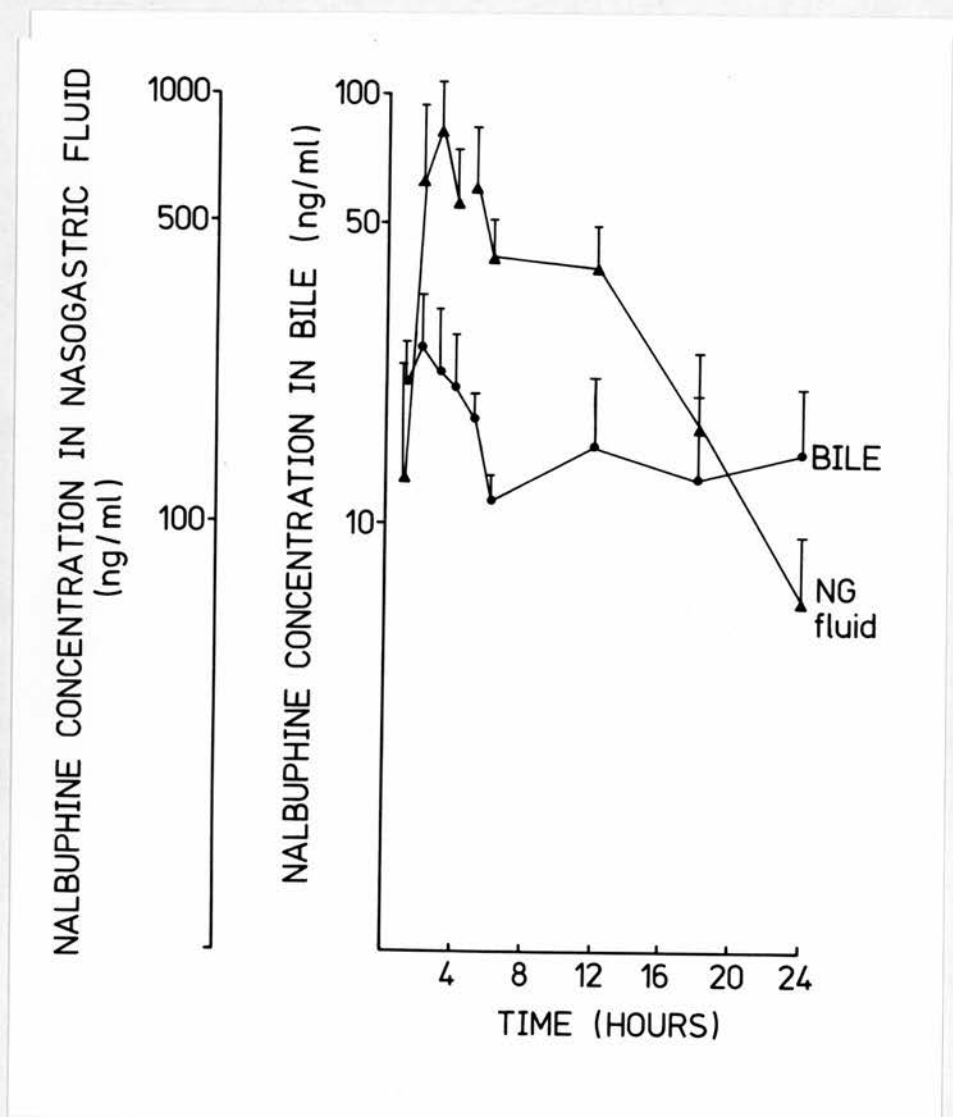


Figure 12.2: Mean (SEM) concentration of nalbuphine in bile and nasogastric aspirate after the administration of 0.15 mg/kg nalbuphine.

CUMULATIVE RENAL EXCRETION

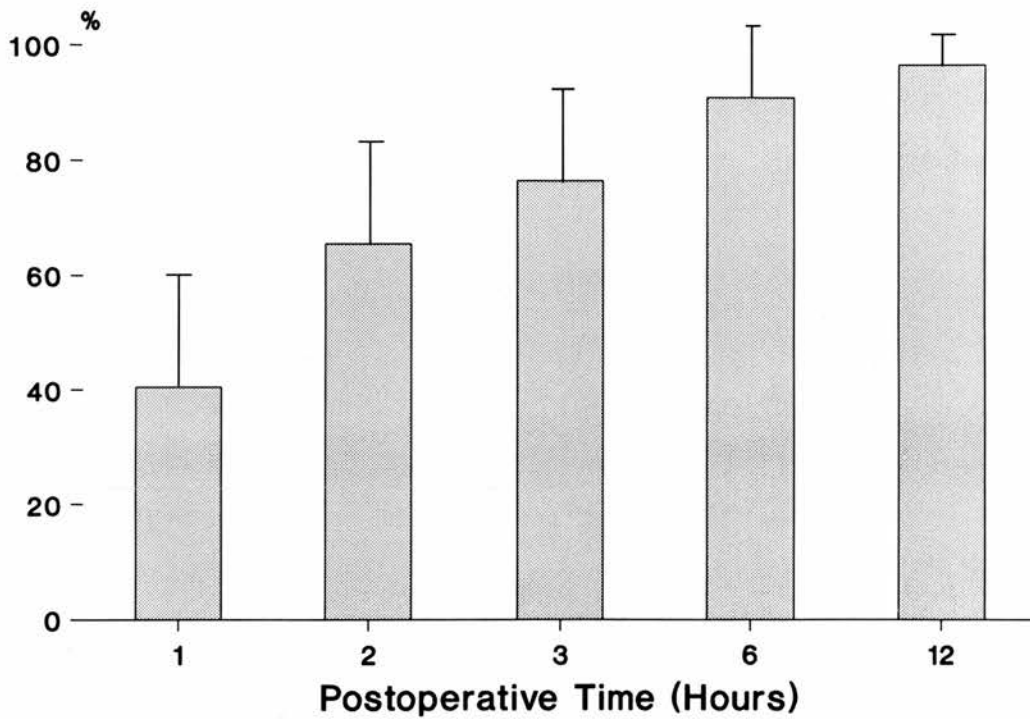


Figure 12.3: The mean (SD) cumulative renal excretion of nalbuphine expressed as a % of the total excreted over 24 hours.

Discussion

The pharmacokinetic data available for nalbuphine before this study were limited to healthy volunteers, fit anaesthetised patients or those undergoing cardiopulmonary bypass (Lake et al 1982b; Sear, Kegan and Kay 1987; Aitkenhead, Lin and Achola 1988). In this study, although interpatient variability was great, the mean elimination half life of 230 minutes is similar to that of 222 minutes reported in healthy volunteers by Aitkenhead and his colleagues (1988), but longer than the mean elimination half life of 135.5 minutes in anaesthetised patients reported by the Oxford group (Sear, Kegan and Kay 1989).

Although the elimination half life, after liver transplantation, was similar to that measured in volunteers, this reflected a decrease in both the clearance and the volume of distribution of nalbuphine, probably due to the effects of surgery and anaesthesia. Reductions in the clearance and volume of distribution have been reported by the Oxford group, although the relative decrease in clearance was greater, thus explaining the shorter elimination half life. Mean residence time was also longer in patients after liver transplantation than in those studied during anaesthesia.

High concentrations of nalbuphine were found in the nasogastric fluid, indicating that nalbuphine is excreted by the stomach. An alternative explanation might be that bile is draining through an open pylorus into the stomach. Since the concentration of nalbuphine in bile was lower than that in nasogastric fluid this is an unlikely explanation. Furthermore, the presence of a T-tube, draining the common bile duct, would have prevented most of the nalbuphine excreted in the bile from reaching the gastrointestinal tract. Gastric secretion of opioids has been previously demonstrated with fentanyl (Stoeckel, Hengstmann and Schuttler 1979).

Only two percent of the drug was excreted in the urine during the study period and the remaining 98% was probably excreted as a metabolite which was not measured. Some unchanged nalbuphine may have been excreted in the faeces as a consequence of gastric excretion, once the postoperative ileus had resolved.

Despite the advantages of nalbuphine as an analgesic it has not become adopted for use in this group of patients. The reasons for this are unclear, but several patients appeared not to obtain satisfactory pain relief and felt nauseated after receiving the drug. The wide variation in pharmacokinetic parameters, which may result in unpredictable behaviour, is a further feature of concern.

CHAPTER 13.

ANALGESIA: REGIONAL TECHNIQUES

Postoperative respiratory complications are common in patients following liver transplantation and good pain relief is an essential part of their prevention. While the patient is receiving artificial ventilation, analgesia can be easily provided by opiates. During weaning from artificial ventilation and when the patient is breathing spontaneously good analgesia is particularly important to prevent splinting of the diaphragm and to enable deep breathing and coughing. A cooperative patient, without respiratory depression, is essential for adequate physiotherapy. Opiates can be used to provide postoperative analgesia; but the surgical incision following liver transplantation is large and in the doses needed to provide adequate analgesia their use may result in depression of consciousness, respiratory depression and suppression of the cough reflex. Intercostal nerve blocks have been shown to be an effective method of providing analgesia following both thoracic and abdominal incisions and may be superior to opiate analgesia, resulting in fewer adverse pulmonary effects (Engberg 1975).

The "Mercedes" incision starting at the xiphisternum and extending down to midway between the xiphisternum and

the umbilicus, with subcostal extensions, makes it necessary to block the intercostal nerves T5-T10 bilaterally. The nerves are usually blocked as they lie in the subcostal groove in the midaxillary line (Lofstrom 1979). The local anaesthetic agent, bupivacaine, is used since it has a long duration of action. Pneumothorax is a rare complication

of their use, occurring in less than one percent of patients after liver transplantation. Despite the low incidence of this risk, and their effectiveness, intercostal nerve blockade is not performed whilst the patient is receiving artificial ventilation because of the risk of a tension pneumothorax.

A pneumothorax occurring during spontaneous ventilation is unlikely to be under pressure, and arterial hypoxaemia is usually the only accompaniment.

Thoracic epidural analgesia, although theoretically offering many advantages, is not employed in this group of patients because of the bleeding disorders frequently encountered in patients with liver disease. An additional risk, when using local anaesthetics (but not opioids) for epidural analgesia, is hypotension due to sympathetic nerve blockade. This may be potentiated in these patients by an abnormal splanchnic circulation. Intrapleural analgesia is effective (Reiestad and Stromskag 1986) but is not used because of the risk of pneumothorax and

of introducing infection into the pleural cavity.

Intercostal nerve blockade is widely used in adult patients both intraoperatively and for postoperative analgesia (Moore 1975) but it is not popular in paediatric practice. It has, however, been suggested for the same indications in children as in adults (Shulte-Steinberg 1980). Small children developing pain from the surgical incision following liver transplantation will often develop marked respiratory distress. The risk of pneumothorax is the main disadvantage of intercostal nerve blockade but its reported incidence in adults varies widely (Moore 1975) and appears to be operator dependent; no incidence has been quoted in children.

Administration of local analgesic blocks to children has a number of problems, particularly for the occasional paediatric anaesthetist (Brown 1985). These include the practical difficulties of dealing with small children; their variations from the more familiar adult anatomy; the different equipment or techniques that may be appropriate and the lack of information regarding the pharmacokinetics of local anaesthetics in paediatric patients. In the awake child, the mobility and distress produced by repeated injections further complicate administration of local analgesic blocks. Since intercostal nerve

blockade conferred significant advantages in adults, the application of this technique was investigated in children. The standard method for intercostal nerve blockade was modified and developed to provide postoperative analgesia to paediatric patients following liver transplantation. I was assisted by Dr Maire P Shelly with the data collection.

INTERCOSTAL NERVE BLOCKADE FOR CHILDREN

Anaesthesia (1987) 42; 541-547

Technique of intercostal nerve block

The technique of intercostal nerve blockade was a modification of that described for adults in the mid axillary line (Lofstrom 1979). The local analgesic used was bupivacaine hydrochloride without adrenaline, 2mg/kg being diluted to give a volume of 1ml for each intercostal space to be blocked. A 100cm length of low dead space manometer tubing was primed with the solution so that a remote needle technique could be used, with a second operator to inject the solution (Winnie 1969). The patient was placed either in the lateral position or supine and firmly restrained. The skin was cleaned and the rib palpated in the midaxillary line. A 25 gauge needle was introduced perpendicularly through the skin, on to the rib and gently walked down the rib to its caudad edge. At this point, the needle was angled posteriorly and

advanced slightly medially and posteriorly so that it was almost parallel to the rib, until the tip of the needle lay 1-2mm beneath the edge of the rib, with the bevel of the needle facing cephalad (Figure 13.1). A loss of resistance was frequently experienced and the needle felt to slide into the subcostal space. Holding the needle firmly in position, with the back of the right hand supported against the patient and the left hand palpating the rib or steadying the needle (Figure 13.2), the assistant holding the syringe was asked to aspirate and, if no blood or air was withdrawn, 1ml of solution was injected and the needle removed.

Patients

Twenty children under the age of ten had undergone liver transplantation at this centre at the time of this study. Intercostal nerve blockade was performed in the immediate postoperative period to facilitate weaning from controlled ventilation. Not all of the children received intercostal nerve blocks during this period either because of the absence of an operator familiar with the technique or because of a continuing need for controlled ventilation. Regional analgesia was routinely supplemented by bolus opiate administration as necessary to relieve visceral pain.

posterior

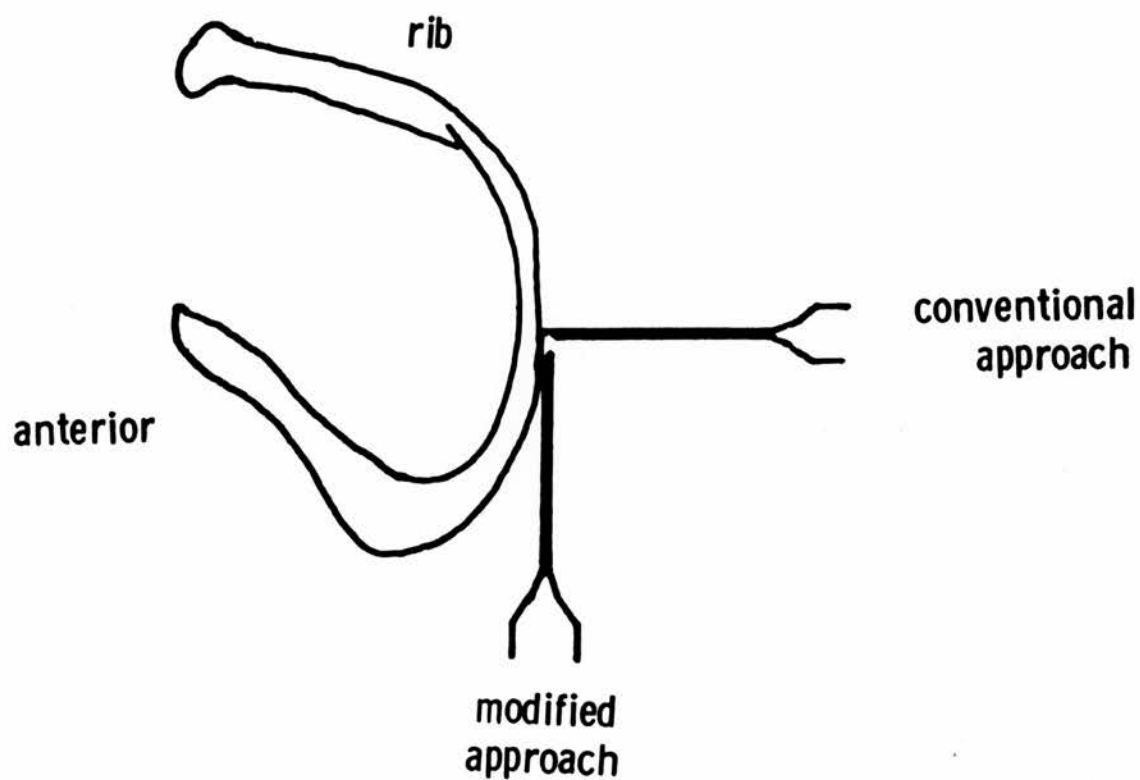


Figure 13.1: Diagram to show the position of the needle relative to the rib when performing intercostal nerve blockade by the conventional and the modified technique.

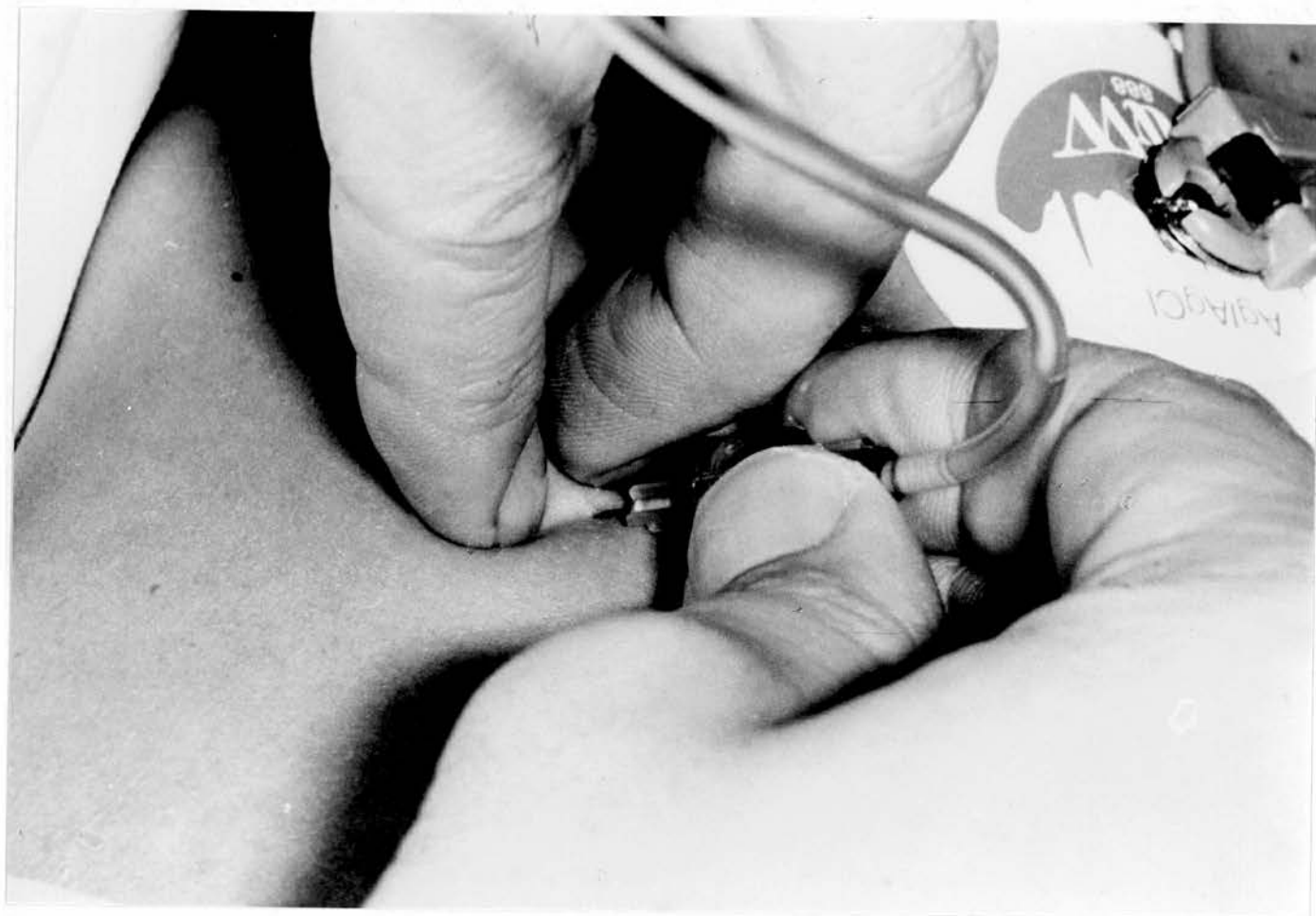


Figure 13.2: The position of the hands and needle during intercostal nerve blockade in children using the modified technique.

The records of all twenty patients were reviewed to assess the efficacy of intercostal nerve blockade in this group and the incidence of any complications. To assess analgesic efficacy, opiate requirements on the third postoperative day were converted to morphine equivalents (Morrison 1970) and expressed as mg morphine/kg for that day. Intercostal nerve blocks were performed on the Intensive Care Unit during the first four days postoperatively. However, the third postoperative day was chosen to assess analgesic requirements because weaning from artificial ventilation had generally been achieved by this time and pain from the surgical incision was still sufficiently severe to impair respiration as well as causing distress. At least one erect chest Xray was taken daily in each child, enabling prompt and accurate identification of any pneumothorax.

Results

Twenty children had a total of 21 operations, one patient undergoing retransplantation in the early postoperative period. Ten of the children received intercostal nerve blockade on a total of 29 occasions after 11 operations, and on each occasion 10 intercostal nerves were blocked. The other ten children did not receive intercostal nerve blockade, analgesia being provided solely by intravenous administration of opiates. Analgesic requirements on the third

postoperative day were not determined for seven patients. Two patients received intercostal nerve blockade as part of their postoperative analgesic regimen but this was omitted on the third postoperative day because no skilled operator was available. The other five patients did not receive intercostal nerve blockade; two had died by the third postoperative day and information for the other three was incomplete and analgesic requirement could not be assessed for that day. The details of the 14 patients whose analgesic requirements were reviewed are summarised in Table 13.1 and shown in greater detail for all children in Tables 13.2 and 13.3. Nine of the patients had received intercostal nerve blockade and were extubated on or before the third postoperative day. Of the five patients who did not receive intercostal nerve blockade, two were extubated on the third postoperative day; the other three were receiving controlled ventilation.

The nine patients who received intercostal nerve blockade required 0.16 (0.27) mg/kg morphine [mean (SD)] on the third postoperative day and five (56%) of these children required no opiate supplements on that day.

	ICB	no ICB
Number	9	5
Age (years)		
: mean	3.7	2.8
: range	1.1-7.0	2.0-3.5
Sex (M:F)	4:5	2:3
Weight (kg)		
: mean	14.2	12.8
: range	10-22	8-22
Diagnosis		
Biliary atresia	6	3
Neonatal hepatitis	1	1
α_1 -antitrypsin deficiency	1	
Drug induced cirrhosis	1	
Angiocarcinoma		1

Table 13.1: Details of the paediatric patients who received intercostal nerve blockade (ICB) and those who did not.

Patient Number	Age (years)	Sex	Weight (kg)	Diagnosis
1	3.5	F	22	Angiocarcinoma
2	7.0	F	24	Idiopathic Cirrhosis
3	2.0	M	12	Biliary Atresia
4	2.0	M	14	Biliary Atresia
5	7.0	F	22	Biliary Atresia
6	3.8	M	15	Biliary Atresia
7	5.8	M	16	α_1 -antitrypsin Deficiency
8	4.5	F	16	α_1 -antitrypsin Deficiency
9	0.7	F	6	Biliary Atresia
10	2.5	M	10	Biliary Atresia
11	6.3	F	15	Neonatal Hepatitis
12	3.0	F	10	α_1 -antitrypsin Deficiency
13	3.5	M	14	Biliary Atresia
14	2.7	F	8	Neonatal Hepatitis
15	4.3	F	18	Biliary Atresia
16	2.0	M	12	Biliary Atresia
17	3.0	F	12	Biliary Atresia
18	5.3	F	17	Tyrosinosis
19	4.0	F	13	Drug induced Cirrhosis
20	1.1	M	10	Biliary Atresia

Table 13.2: Details of the first 20 children who underwent liver transplantation after 1983.

Patient No	ICB Number	Opiate Need	Ventilation Mode	Total ICB
1	0	2.2	SV	0
2	N/A			
3	2	0.79	SV	3
4	2	0	SV	3
5a	0	0.6	SV	2
5b	2	0	SV	3
6	Died			
7	Died			
8	N/A			
9	N/A			
10	0	0.33	CMV	0
11	2	0.04	SV	2
12	1	0	SV	3
13	1	0	SV	3
14	0	0.7	CMV	0
15	1	0.41	SV	1
16	0	2.09	CMV	0
17	0	2.3	SV	0
18	0	0.58	SV	3
19	0	0.21	CMV	0
20	1	0	SV	2

Table 13.3: Opiate requirement of all 20 patients on the third postoperative day (morphine equivalents mg/kg). CMV = continuous mandatory ventilation, SV = spontaneous ventilation.

All patients who did not receive intercostal nerve blockade received opiate analgesia. On the third postoperative day, the patients who did not receive intercostal nerve blockade required 1.52 (0.93) mg/kg morphine. The three patients still requiring controlled ventilation on the third postoperative day had more severe illness and were sedated with midazolam in addition to morphine. They received a mean of 1.04 mg/kg morphine on that day; the two patients extubated on the third postoperative day, however, received a mean of 2.25 mg/kg morphine on that day. Most of the children received intercostal nerve blockade on two or three occasions during and after weaning from artificial ventilation. The duration of analgesia on each occasion was approximately 12 hours.

The complication rate of this technique was low. Although two of the twenty children developed a unilateral pneumothorax, one child had not received intercostal nerve blockade and the other had received intercostal nerve blockade three days previously and was the first patient on whom the technique was performed. The patients frequently slept after administration of the blocks, but none had evidence of systemic local anaesthetic toxicity. Two patients developed sputum retention after early discharge from the Intensive Care Unit. Both received intercostal nerve

blockade initially but were subsequently given relatively high doses of morphine for analgesia and sedation on the ward.

Discussion

Children undergoing liver transplantation are a small but uniform group, each having the same operation performed through the same incision. In children, few other abdominal procedures are performed that require the same degree of effective analgesia to relieve severe postoperative pain over a prolonged period. Intercostal nerve blockade has been shown to reduce postoperative opiate requirements and respiratory impairment (Shulte-Steinberg 1980). The main disadvantage of intercostal nerve blockade is the incidence of pneumothorax and, in children, the smaller anatomical distances involved may increase this risk. In the technique described above, a mid axillary approach is used to reduce the likelihood of pneumothorax (Brown and Feik 1979) and since the needle enters the intercostal space at an acute angle, almost parallel to the rib, the risk of pleural puncture is further decreased.

The importance of avoiding the respiratory depressant effects of opiates is illustrated by the two children who developed sputum retention due to sedation following opiate analgesia.

This study reports only a small number of patients but use of intercostal nerve blockade immediately prior to weaning from artificial ventilation, and repeated as necessary afterwards, has reduced opiate requirements significantly during this period and diminished the incidence of problems associated with their use. The complications of intercostal nerve blockade include pneumothorax, haematoma formation and local anaesthetic toxicity from inadvertent intravascular injection. Only one child who received intercostal nerve blockade suffered a small unilateral pneumothorax and that three days after his last intercostal nerve blockade. Since he was the first patient to receive intercostal nerve blocks, this may reflect lack of experience of the technique; no subsequent patient developed this complication. Pneumothorax is a complication of artificial ventilation itself, particularly in children, and one other child who did not receive intercostal nerve blockade also suffered a unilateral pneumothorax. The pneumothorax in this patient was associated with barotrauma during controlled ventilation of noncompliant lungs following the development of the respiratory distress syndrome after inadvertent administration of cyclosporin into a central vein (Powell-Jackson et al 1984). The incidence of pneumothorax was 3.5% in those children who received intercostal nerve blockade.

All patients had slightly impaired clotting indices at the time of their intercostal nerve blockade but neither bleeding nor haematoma formation proved to be a problem. Systemic local anaesthetic toxicity was not observed. Although a maximum bupivacaine dose of 4mg/kg has been recommended (Rothstein et al 1982), a dose of 2mg/kg was administered to these patients because of their impaired liver function. Sleep following intercostal nerve blockade was a consistent feature. This may be due to several factors; sedation is a side-effect of local anaesthetic agents and may be particularly apparent when relatively large doses are used or when rapid uptake occurs, satisfactory analgesia may cause a tired child to sleep and finally, performing the blocks or subsequent physiotherapy may itself tire the child. Although sleepy, the children were always rousable and cooperative. No other complications of the procedure have been noted and the children appeared to forget quickly the temporary discomfort of the repeated injections. The modified technique of intercostal nerve blockade described has been found to provide effective postoperative analgesia with a reduction in opiate requirements in children following liver transplantation. The technique may also benefit other children undergoing thoracic or abdominal surgery.

Although intercostal nerve blockade is effective in

children, the multiple injections do cause them distress. Different ways of alleviating this discomfort were therefore investigated.

At the time this problem was being considered Astra Pharmaceuticals Ltd introduced EMLA cream into the United Kingdom. This cream is a eutectic mixture of two local anaesthetics, prilocaine and lignocaine. The eutectic phenomenon is a spontaneous lowering of the melting point of two substances when they are mixed together. When prilocaine and lignocaine are mixed together their melting points are brought into the range of room temperature, allowing a much higher concentration of both to be achieved. The final concentration of each agent is 25 mg/ml which is sufficiently high to enable penetration of intact skin. Without the eutectic phenomenon both local anaesthetic agents, in this concentration, would crystallise at room temperature. The mixture is combined with arlatone, an emulsifier, and carbapol, a thickener.

When applied to the skin EMLA has been shown to decrease the pain of venepuncture for intravenous induction of anaesthesia (Cooper et al 1987; Hopkins, Buckley and Bush 1988) and for obtaining venous blood specimens (Wahlstedt et al 1984; Clarke and Radford 1986). Furthermore it has been shown to be as effective as infiltration analgesia (using lignocaine) for providing

adequate surgical analgesia for split skin grafting (Goodacre et al 1988). A small pilot study, using EMLA applied before intercostal nerve block, was performed to attempt to reduce some of the discomfort felt by these children.

THE USE OF EMLA CREAM TO REDUCE THE DISCOMFORT OF INTERCOSTAL NERVE BLOCKS

Patients and Methods

At least 60 minutes before the planned time of intercostal nerve blocks one tube of EMLA cream was applied to both sides of the chest in the midaxillary line so as to overlie the site of injection of the intercostal nerve blocks. The cream was then covered with an occlusive dressing. The nerve blocks were performed in the manner described above. Six children were studied.

It became apparent that although the skin was anaesthetised there were other components to the pain of intercostal nerve blockade in these children. In a later study, when I received an intercostal nerve block, it became apparent that there are three components to the pain produced by intercostal nerve blockade. These are:

1. The needle passing through the skin. This is readily blocked by EMLA cream.

2. Some discomfort is experienced when the needle strikes the rib, due to periosteal stimulation.

3. As the local anaesthetic tracks posteriorly in the subcostal groove discomfort is experienced. This may be because the solution is cold and as a consequence causes irritation to the nerves in the subcostal groove. Alternatively, the fluid may separate tissues away from the rib and in so doing produce significant pain. Which tissues are separated is not clear. If the periosteum is stripped from the rib, this would explain the pain, but this is unlikely because of the method of insertion of the needle and the ease with which it is felt to slip along the subcostal groove. A further explanation is that the normal anatomy of the vascular structures and nerves found in the subcostal groove is disrupted, with the resultant stretching of their attachments, causing pain.

One further disadvantage of this technique is that unless great care is taken the operators' fingers become analgesic. Since the use of EMLA cream did not appear effective its use was not pursued further. Reports from Stoke-on-Trent (Seddon and Clayton 1984) of the efficacy of performing intercostal nerve block by jet injection led to an investigation of its use after liver transplantation.

The compressed gas injector gun has been available for

some time and is principally used for mass inoculation. Its use has also been evaluated for inferior dental nerve blockade (Sowray 1981), for paracervical blockade (McKenzie and Shaffer 1978; Kovacs 1982) and for the administration of low dose heparin (Black, Nagle and Strachan 1978). It utilises pressurised carbon dioxide, drawn from a cylinder in the handle, to drive up to 1ml of the solution through a nozzle. As the solution passes through the nozzle it is broken up into particles, each six thousandths of an inch in diameter (Figure 13.3). The speed and size of each particle allow it to travel through skin and a considerable distance into the tissues. Cooke and his colleagues (1980) have shown that the bioavailability of lignocaine using jet injection is the same as that when it is administered using a needle and syringe.

The use of a compressed gas gun for intercostal nerve blockade was claimed to offer several advantages over the conventional needle technique including:

- a. The risk of pneumothorax is eliminated since the pleura is not penetrated. This may enable intercostal nerve blockade to be performed even while the patient is receiving artificial ventilation.

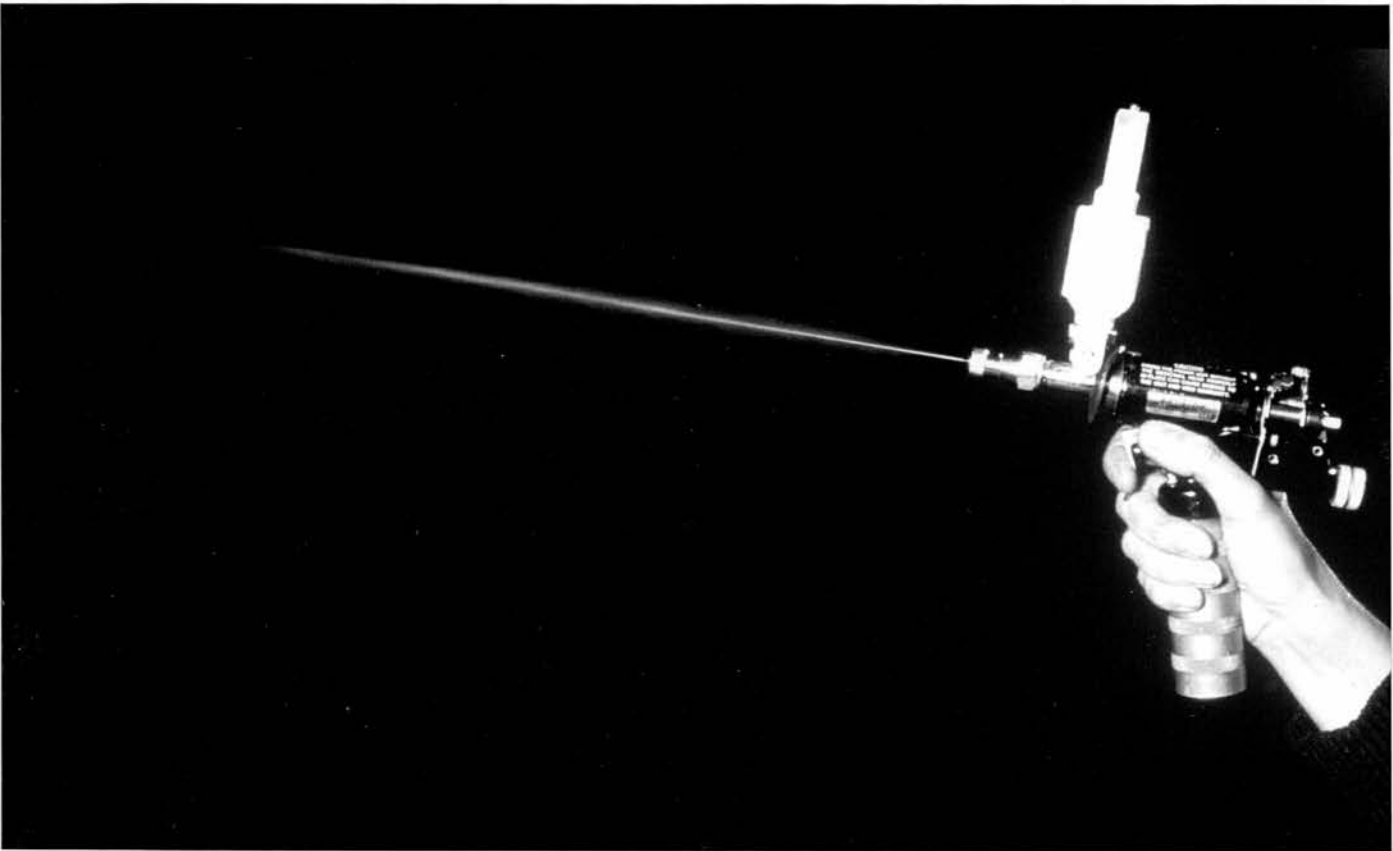


Figure 13.3: The Med-E-Jet gas powered injector gun.

b. Damage to blood vessels is reduced since they are moved aside by shock waves generated by the gun. This would be a particular advantage in patients with a coagulopathy.

c. Since no needles are involved in the technique, patient acceptability of the procedure may be increased, particularly in children.

The main disadvantage of the gas injector is that only small volumes (<1ml) can be used. In the initial study, in adults, Seddon and Doran (1981) used 0.5% bupivacaine for intercostal nerve blockade following thoracotomy and demonstrated some benefit, although they felt that better results could be obtained with a higher concentration of local anaesthetic. In a further study, also in adult patients who this time required cholecystectomy, Seddon and Clayton (1984) used a higher concentration of bupivacaine (1.5%) and obtained better results. Astra Pharmaceuticals Ltd were approached before investigating this method, but would not release bupivacaine of this concentration because of lack of information about its neurotoxicity. However, since this study was to be performed in children, with their smaller dose requirements, it was felt this volume of 0.75% bupivacaine solution should produce analgesia, if the method is effective.

**AN EVALUATION OF THE EFFICACY OF A COMPRESSED GAS
INJECTOR GUN FOR INTERCOSTAL NERVE BLOCKADE.**

Patients and Methods

Four consecutive patients, both adults and children, requiring intercostal nerve blocks after liver transplantation were studied. Informed verbal consent was obtained from the patient and/or their parent. When the patient was ready to be weaned from artificial ventilation a set of intercostal nerve blocks was performed using the established needle injection method, since there is a clinical need for good analgesia at this time. The technique of intercostal nerve blockade was then alternated between the needle method and the gas injector gun. Bupivacaine 0.5% was used when the needle technique was employed and bupivacaine 0.75% with the gas injector gun. Intercostal nerve block using the gas injector gun was performed by palpating the inferior aspect of the rib in the midaxillary line and placing the nozzle of the gun firmly against the skin and perpendicular to it. One ml of 0.75% bupivacaine was then injected. On the occasions the gas injector gun was not used a 23 gauge needle was used to inject 2-3 mls of 0.5% bupivacaine (unless the total dose exceeded 2mg/kg when 0.25% bupivacaine was used) in the midaxillary line (Lofstrom 1979).

A note was made of the duration of analgesia produced by

the two techniques and any requirement for additional analgesia. Bruising or haematoma formation at the site of administration was also noted. Clinical evidence of a pneumothorax was sought after each set of intercostal nerve blocks.

Results

All the patients studied were unanimous after the first attempt to produce intercostal nerve blockade using the gas injector gun that they did not want to experience it again; the noise and percussion on the chest wall frightened the patients. It is of note that in the two previous studies the majority of patients were receiving general anaesthesia when the intercostal nerve blocks were performed (Seddon and Clayton 1984; Seddon and Doran 1981) and this problem would not have been noted.

Bruising and bleeding from the site where the nozzle was placed was considerable. In some instances the entry of the fluid under pressure appeared to have torn the skin. Haematoma formation also occurred, indicating that some blood vessels had been disrupted. These features highlight the frail nature of these very ill patients. Analgesia produced by the injector gun was unsatisfactory and did not last for more than 2 hours.

The absence of adequate analgesia compared with the favourable reports in the previous publications was

surprising and a radiographic study was performed comparing intercostal nerve blockade using a needle and injection using the compressed air gun. In this study Dr Maire P Shelly performed the intercostal nerve block using the gas injector gun, Dr M J Lindop (Consultant Anaesthetist) performed the two intercostal nerve blocks using the standard needle injection method and Dr A Dixon (Consultant Radiologist) performed the computerised tomography scan. I was the volunteer.

***A RADIOGRAPHIC AND CADAVERIC STUDY
OF THE GAS INJECTOR GUN***

Intercostal nerve blockade was performed using the gas injector gun on the sixth rib on the right side. One ml of a solution containing 10% lopamidol was injected and a computerised tomography scan of that area was undertaken. The results are shown in Figure 13.4.

Two further intercostal nerve blocks were performed on the tenth ribs on both sides using the conventional adult method (Moore 1975). The lower site was chosen to be below the reflection of the pleura and so decrease any risk of pneumothorax to the volunteer. One ml of a solution containing 10% lopamidol was injected so that the subsequent CT scan would be as similar as possible to the previous study. The results of this study are shown in Figure 13.5.

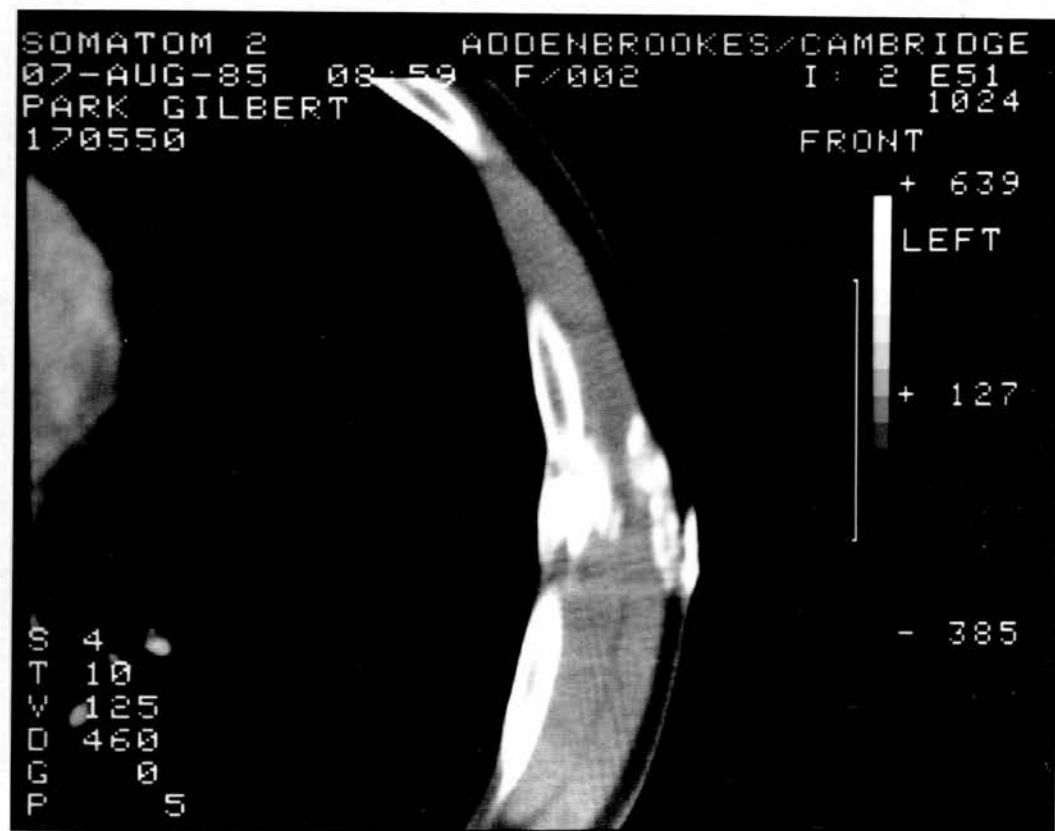


Figure 13.4: Computerised tomography scan after 1 ml 10% lopamidol injected using the compressed gas jet injector gun into the subcostal groove of the sixth rib.

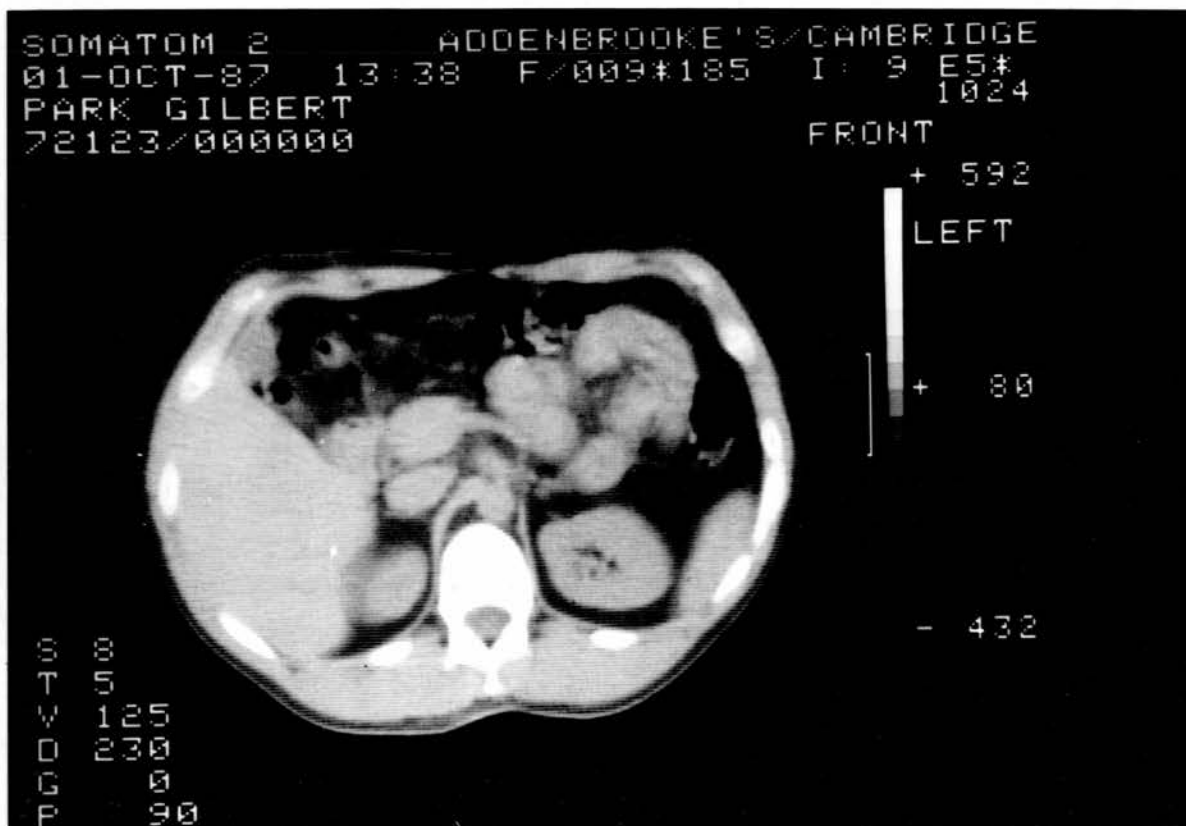


Figure 13.5: Computerised tomography scan after 1 ml of 10% lopamidol has been injected into the subcostal groove of the tenth rib using needle injection.

When the two sets of CT scans are compared it is apparent that significant differences in the disposition of the radio-opaque dye are seen. With the gas injector gun contrast medium is seen lying under the skin and diffusely spread throughout the subcutaneous tissue. Only a small amount has been deposited in the subcostal area. The pleura is seen to bulge (a feature previously noted in the original description (Seddon and Doran 1981) of the technique) and there is discontinuity between the subcutaneous and the subcostal dye, indicating haematoma formation . When the CT scan from the intercostal blocks performed using a needle is studied, contrast medium is seen to be predominantly deposited in the subcostal area, with little in the subcutaneous tissue. Furthermore, contrast medium is seen to spread along the rib.

To further examine the disposition of local anaesthetic solutions, a cadaver study was performed. Methylene blue was injected through the skin using the gas injector gun as previously described. This section of rib was removed and shown in Figure 13.6. It can be seen that dye lies over the outer aspect of the rib cage and Figure 13.7 shows the rib from the medial aspect with little bulging of the pleura. It is important to note that no spread of dye was seen anteriorly or posteriorly from the site of injection.

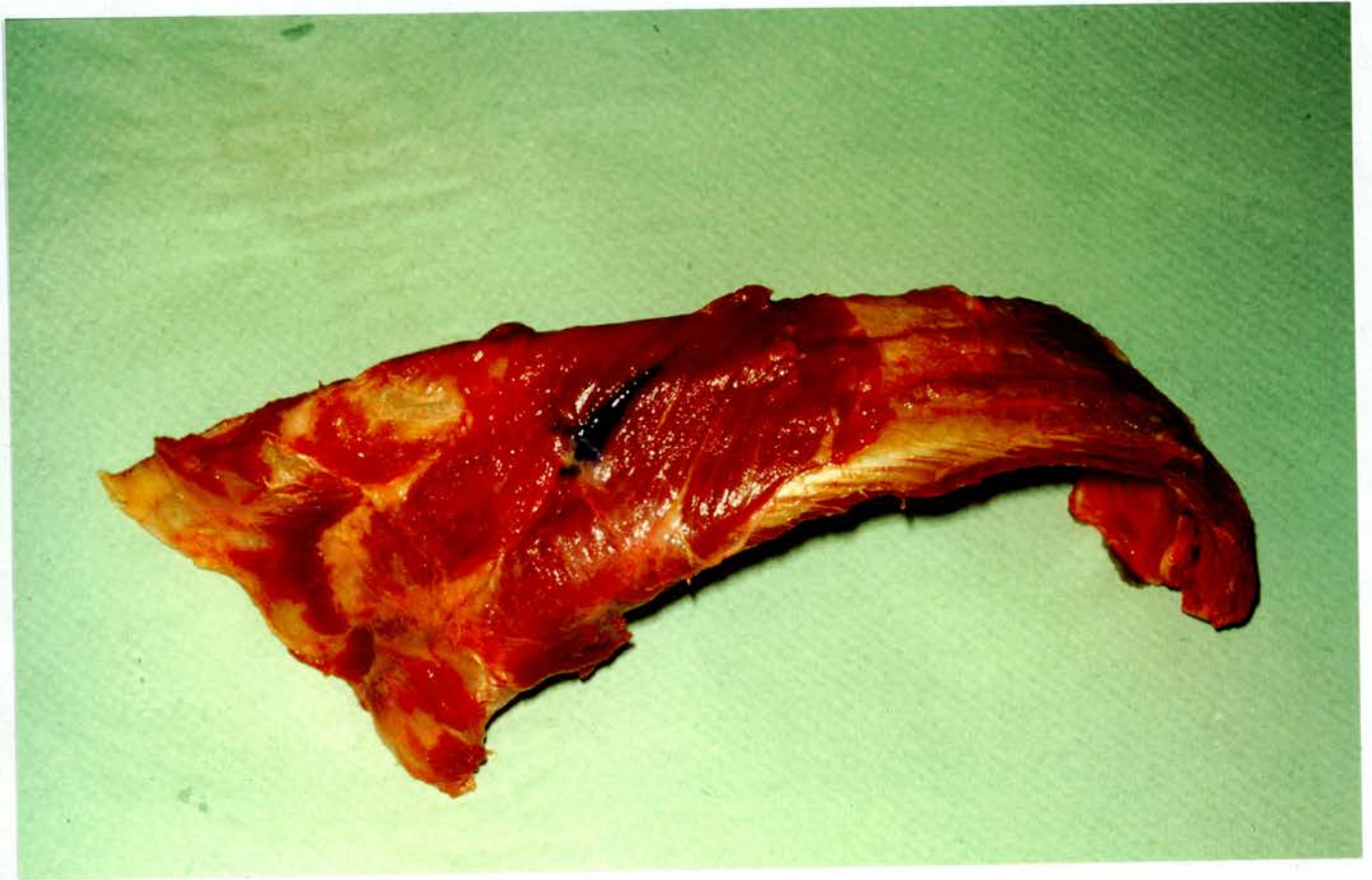


Figure 13.6: Section of the thoracic wall viewed from the outside after 1ml of methylene blue has been injected using the gas injector gun.

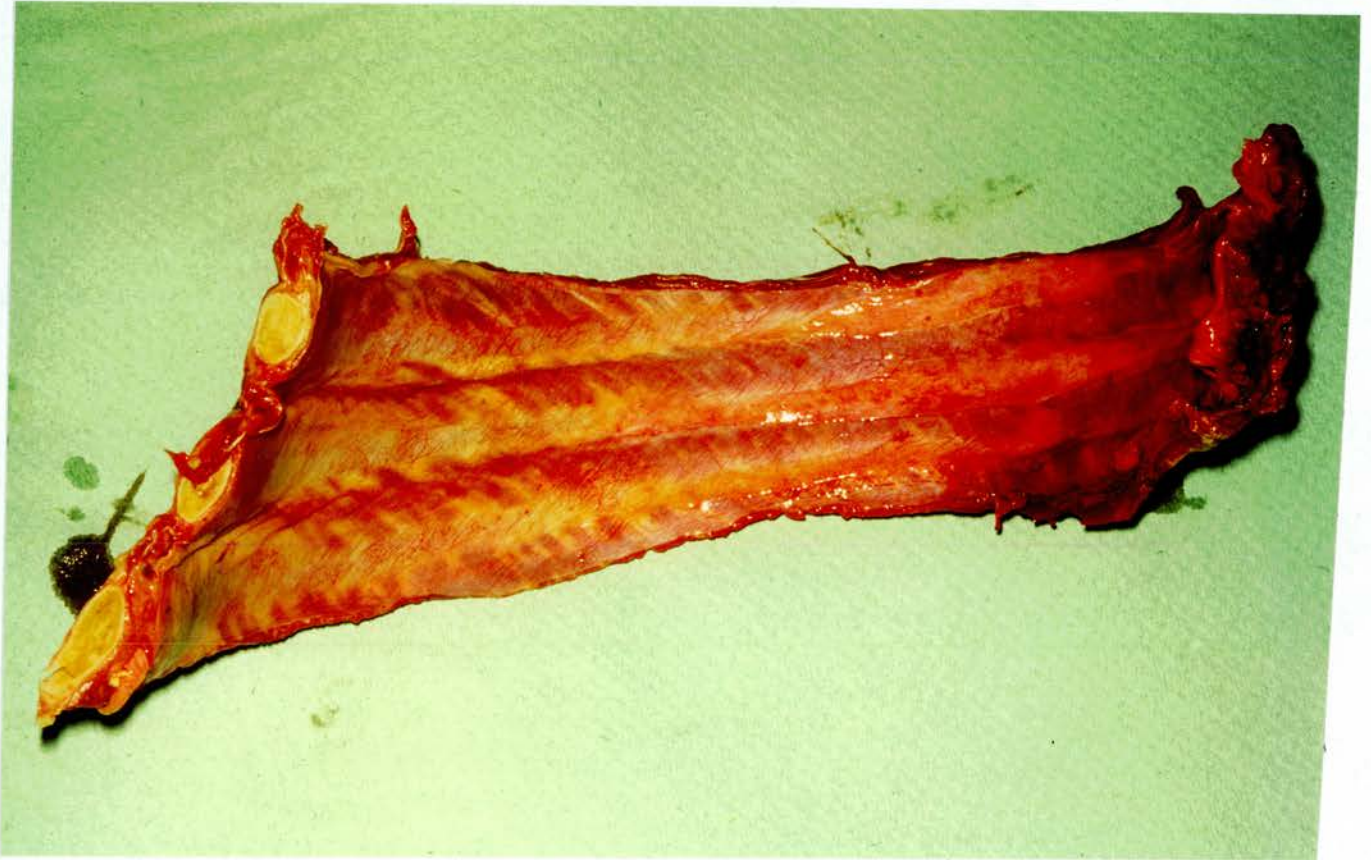


Figure 13.7: Section of the thoracic wall viewed from within the pleural cavity after injection of 1ml of methylene blue using the gas injector gun.

Both the CT and cadaver study demonstrate that the disposition of local anaesthesia is very localised following administration using the gas injector gun, with little lateral or medial spread, compared with injection using a needle. This may be an explanation of why inadequate analgesia was obtained with this method. Three studies, using needle injection in cadavers and patients, have demonstrated the spread of the local anaesthetic solution from the site of injection both medially and laterally (Murphy 1984; Nunn and Slavin 1980; Moore, Bush and Skulock 1980). Murphy (1984) and Nunn and Slavin (1980) suggested that spread of local anaesthetic solutions cephalad and caudad may also be an important mechanism in the analgesia provided by intercostal nerve blockade, although Moore (1981) strongly contests that. A further mechanism involves inadvertent intraneural injections during intercostal nerve blockade resulting in a spinal nerve block (Selander and Sjostrand 1978). The importance of spread by all of these mechanisms is emphasised when variations in the position of the proximal intercostal nerve are considered (Hardy 1988). In addition, significant haematoma was associated with use of the gas injector in patients and it was also demonstrated on the volunteer CT scan in the area of the injection. This latter feature will dilute the concentration of local anaesthetic solution in the area of the intercostal nerve. All of these factors may contribute to the lack

of efficacy of the gas injector gun in patients.

Since this method did not provide satisfactory analgesia a further method using direct wound perfusion with local anaesthetic solutions was evaluated.

Wound perfusion with a local anaesthetic solution might be expected to produce a decrease in opiate requirement not only by its effect on pain fibres, but also by diluting pain producing substances, such as bradykinin and histamine in the wound. The first study of the direct perfusion of surgical wounds with local anaesthetic solutions was reported by Cappelle in 1935 (Levack, Holmes and Robertson 1986) and subsequently by Blades and Ford (1950) for thoracotomy incisions. Both investigators noted a decrease in opiate requirements. Other investigators looked at direct wound infiltration with local anaesthetic solutions and similarly noted a decrease in opiate requirements (Gerwig, Thompson and Blades 1951; Lewis and Thompson 1953). Although opiate requirements were again reduced none of these studies was controlled. This method was more fully investigated by two groups on patients following cholecystectomy (Thomas, Lambert and Lloyd Williams 1983; Levac, Homes and Robertson 1986). Both groups randomly allocated patients to receive bupivacaine or saline placebo and observers and patients were blind to the nature of the solutions. Their findings were also similar; those patients who received

bupivacaine wound perfusion having a similar decrease in opiate requirements to those patients who received saline perfusion. In the trial by Levac and his colleagues (1986), however, there was a significant reduction in the forced vital capacity of the placebo group compared with the group receiving bupivacaine, possibly indicating some decrease in wound pain during deep breathing.

DIRECT WOUND PERFUSION WITH LOCAL ANAESTHETIC SOLUTIONS

Patients and Methods

To investigate any advantage of this simple technique in patients following liver transplantation, three modified infusion catheters with attached microbiological filters were inserted into each limb of a Mercedes incision (Figure 13.8). In the two previous studies (Thomas, Lambert and Lloyd-Williams 1983; Levac, Holmes and Robertson 1986) a wound drainage catheter was used to place local anaesthetic solution into the wound. These catheters have large holes to permit drainage and have a low resistance to flow at each orifice. When local anaesthetic is injected any local obstruction will tend to increase the resistance at that orifice, leading to preferential flow out of other portions of the catheter and patchy anaesthesia. For the purposes of this study a specially designed and made catheter was used [supplied by Portex (Hyde, Kent)] which had orifices made by

puncturing the catheter with the tip of a sewing needle in the first 10 cm of their length. There was no end orifice. Since the catheter was made of a soft pliable plastic these orifices only open when fluid is injected. The small orifices in the catheter gave a high resistance to flow and thus a partial obstruction did not prevent flow out of that slit. This ensures even distribution of local anaesthetic solution along the terminal 10 cm portion of the catheter without pooling (Figure 13.9).

A formal clinical trial was proposed and ethical approval obtained. However, before proceeding with the study a pilot study was performed. After weaning was complete (initial analgesia having been provided with intercostal nerve blocks) and when the patient next felt pain 10 ml of 0.25% bupivacaine was injected into each infusion catheter. Patients were observed for pain relief (decrease in respiratory and heart rate, change in facial grimacing etc) and asked to cough and comment on pain relief. Three patients were studied in this open way and following the infusion of bupivacaine no physiological change, or increase in the ability to cough or relief in pain, was noted in any patient. Although the risk of infection was diminished by the microbiological filters it was felt still to be present and particularly hazardous in an immunosuppressed patient receiving corticosteroids.

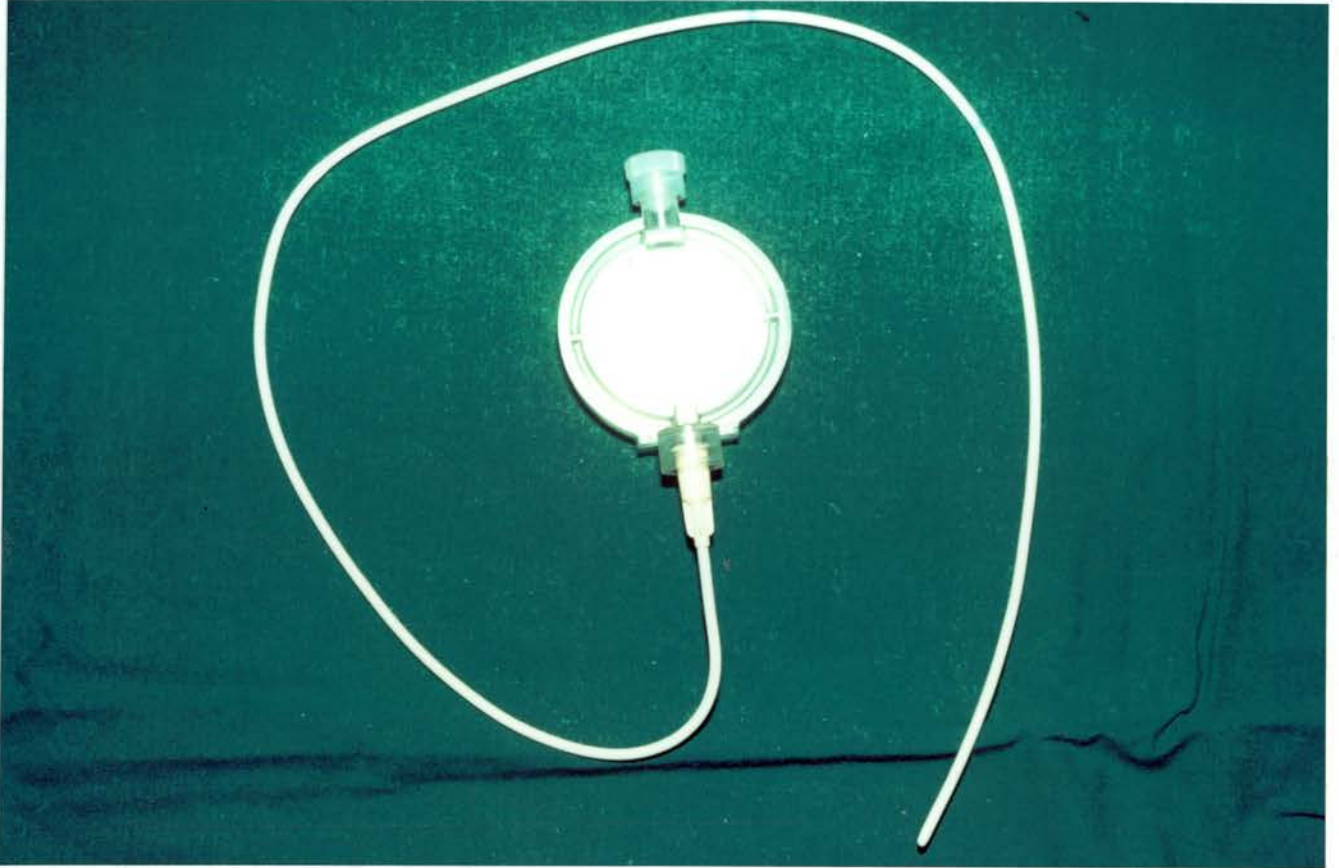


Figure 13.8. Wound perfusion catheter with attached microbiological filter.



Figure 13.9. Small orifices in the wound perfusion catheter. A 10ml syringe, filled with water has been attached to the filter/catheter. The water is then being injected which requires the application of some pressure to the syringe.

Since an open trial did not show any benefit and there appeared to be a small risk to the patient the proposed trial was abandoned. It is of note that subsequently others (Chester et al 1989) claim to have shown some benefit from a prospective, placebo-controlled study of wound perfusion catheters. On the first postoperative day after cholecystectomy the patients' analgesic demands for pethidine were identical, irrespective of whether they received bupivacaine or placebo, but the group receiving the bupivacaine had lower pain scores.

It would appear that if regional analgesia is to be used there is no suitable alternative to intercostal nerve blockade. To prevent distress in children, low dose ketamine can be administered immediately prior to intercostal nerve block.

Having decided that intercostal nerve blocks are the most suitable form of regional anaesthesia, it became apparent that there was only limited data about the use of local anaesthetic agents in patients with liver disease. The long duration of action of bupivacaine makes it the drug of choice for intercostal nerve blockade. Bupivacaine is metabolised by the liver, with a lower hepatic extraction ratio than lignocaine (Tucker and Mather 1979; Tucker et al 1977). Clinical studies have shown that clearance of lignocaine, the other commonly used amide local anaesthetic, may be impaired

in cirrhotic patients (Thompson et al 1973), after hepatectomy (Aldrete et al 1970), and during viral hepatitis (Williams et al 1976). No such data exists for bupivacaine. Furthermore, patients with severe liver disease develop portal hypertension and extensive collateral vessel formation. The effect of these enlarged vessels on the speed of drug absorption was not known.

Total plasma concentrations of bupivacaine were therefore measured after intercostal nerve blockade in patients who had recently undergone liver transplantation. Since bupivacaine is bound to α_1 -acid glycoprotein (AAG), this was also measured.

I was assisted in this study with the sample collection by Dr A Bodenham, the bupivacaine assays by Mr J Goudie (Department of Biochemistry, St Albans City Hospital) and the AAG assays by Dr Jacqui Calvin (Department of Clinical Biochemistry, Addenbrookes Hospital).

**PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER INTERCOSTAL
NERVE BLOCKADE IN PATIENTS FOLLOWING ORTHOTOPIC LIVER
TRANSPLANTATION.**

British Journal of Anaesthesia 1990 64; 436-441

Patients and Methods

Eleven patients who required analgesia on the first or second day after liver transplantation were consecutively divided into two groups:

Group 1 included 6 patients having a single set of bilateral intercostal nerve blocks using plain bupivacaine (2mg/kg).

Group 2 consisted of 6 studies in 5 patients having two sets of bilateral intercostal nerve blocks separated by 6 hours using bupivacaine plus adrenaline 1/200,000 (2mg/kg on each set of injections). One patient was studied on two occasions 4 months apart after her first and second liver transplant.

The intercostal nerve blocks were performed when the patient was ready for tracheal extubation, usually on the first postoperative day. A baseline blood sample was withdrawn from a radial arterial cannula, previously inserted for other purposes. Bilateral intercostal nerve blocks (T5-T10) were then performed using the standard technique described earlier. A total

dose of 2mg/kg bupivacaine with or without adrenaline was injected on each occasion. In smaller, wasted patients the dose of bupivacaine was made up to a minimum volume of 30 ml allowing an adequate volume of solution. Arterial blood (5ml) was then sampled at 5, 10, 15, 30, 60, 120, 240 and 480 minutes after the injection of bupivacaine. In group 2 the sampling protocol was slightly changed with an extra sample taken at 2.5 minutes and the final sample taken at 360 minutes, immediately before the intercostal blocks were repeated, following which the sampling procedure was repeated.

Blood was collected in tubes containing lithium heparin as an anticoagulant and separated by centrifugation at 3000 rpm. Plasma was then stored at -20°C until analysis. Liver function tests (albumin, total protein and α_1 -acid glycoprotein) were also measured from a baseline serum sample. Any adverse reactions such as blood pressure changes or neurological deterioration were recorded during this period. Detailed neurological assessment was not possible due to residual opiate and benzodiazepine effects and the process of tracheal extubation.

Bupivacaine concentrations in groups 1 and 2 were compared by Student's t test for paired data. The relationship between bupivacaine concentrations and AAG

concentrations was determined using analysis of linear regression.

Analysis of samples

The assay was performed using HPLC as described by Nation and his colleagues (1979). After the addition of an internal standard (etidocaine), the sample was alkalinised with sodium hydroxide and extracted with dichloromethane. An aliquot of extract was evaporated to dryness at 50°C and redissolved in a mobile phase of 1% triethylamine in water, adjusted to a pH of 3.0 with phosphoric acid and organic modifier (30% acetonitrile) prior to injection. The solution was injected into a 150 x 4.6 mm column containing 5 micrometre ultrasphere "ods" and the flow rate was adjusted to 1.5 ml/min at ambient conditions. An ultraviolet detector at 205nm was used. The assay was calibrated with spiked standards. To exclude interference from the other drugs patients received during their period of intensive care, control samples of serum from other liver transplant recipients, who had not received bupivacaine were analysed and showed no interference with the assay. In addition to this study, a further 2000 samples have been analysed, and no interference from other substances detected. The sensitivity of the assay was 50 ng/ml with a within-batch variation of 3.9% and a between-batch variation of 4.0%.

The AAG assay was performed by an automated turbidimetric immunoassay using an IL Monarch analyser utilising "Dako" antiserum to AAG.

Analysis of areas under the concentration time curves were performed using an "Apple Fitter" programme. The values for elimination half life and clearance in this study were not calculated, as sampling was not carried out for the recommended three elimination half-lives owing to the need to repeat the injections for analgesia.

Results

The details of the 11 patients studied are shown in Table 13.4.

The injections were performed a mean time of 15.7 (8.5) hours [mean (SD)] after the transplanted liver had been reperfused. The concentrations of plasma proteins and liver function tests at the time of each study are listed in Table 13.5.

The mean time to complete the bilateral intercostal nerve blocks was 4.5 (1.8) minutes. The mean (SEM) total plasma concentrations of bupivacaine in the two groups plotted against time are shown in figures 13.10 and 13.11.

Patient	Age	Sex	Weight	Presenting diagnosis
	(yrs)	M/F	(kg)	
<u>Group 1</u>				
1.	17	F	55	Chronic active hepatitis.
2.	56	F	45	Primary biliary cirrhosis.
3.	39	M	67	Sclerosing cholangitis.
4.	58	F	37	Primary biliary cirrhosis.
5.	29	F	60	Alcoholic cirrhosis.
6.	45	F	54	Primary biliary cirrhosis.

Group 2

7.	26	F	55	Primary biliary cirrhosis. (Patient studied twice after two separate transplants)
8.	52	M	80	Alcoholic cirrhosis + hepatoma.
9.	40	F	68	Chronic rejection of previous transplant for sclerosing cholangitis.
10.	59	F	64	Primary biliary cirrhosis + polycystic disease.
11.	21	F	43	Wilson's disease.

Table 13.4: Demographic data and presenting diagnosis of the patients in groups 1 and 2.

Patient	Albumin (g/l)	Total protein (g/l)	AAG (g/l)	Bilirubin (μ mol/l)	ALT (U/l)	AP (U/l)
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Group 1

1.	46	58	0.9	108	610	43
2.	37	67	0.9	150	534	206
3.	20	80	0.7	123	78	179
4.	35	74	2.3	62	684	783
5.	24	55	0.7	14	371	180
6.	25	63	2.4	59	456	1200

Group 2

7.	27	51	1.4	867	115	978 *
	31	45	1.6	249	674	963 **
8.	32	53	1.4	368	506	173
9.	40	62	1.7	100	969	271
10.	38	61	1.1	109	547	200
11.	31	45	1.5	18	34	30

* 1st transplant ** 2nd transplant

Table 13.5: Concentrations of plasma proteins and liver function tests in the 11 patients studied.

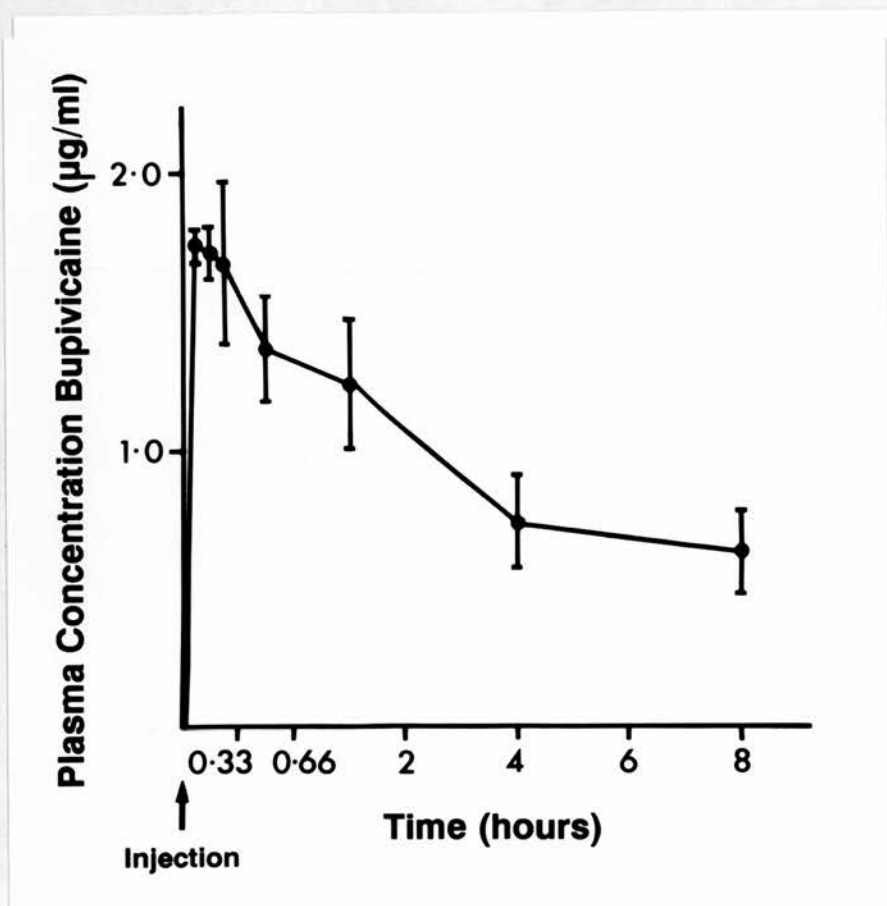


Figure 13.10: Plasma concentrations of bupivacaine [mean (SEM)] in group 1 after a single set of intercostal injections using 2mg/kg bupivacaine.

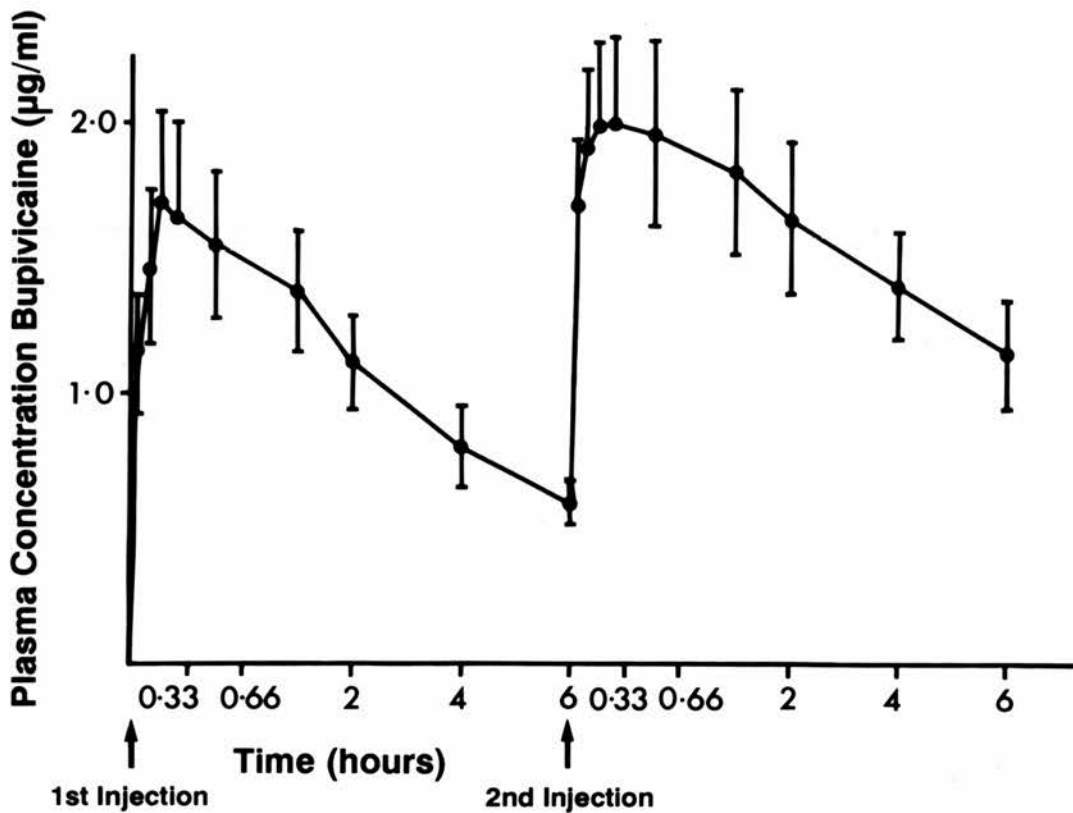


Figure 13.11: Plasma concentrations of bupivacaine [mean (SEM)] in group 2 after a 2 sets of intercostal injections 6 hours apart using 2mg/kg bupivacaine containing 1/200,000 adrenaline.

In group 1 (plain bupivacaine) the mean (SEM) maximum concentration (C_{max}) was 1.75 (0.07) µg/ml. The time taken to reach C_{max} (T_{max}) occurred at 5, 10 and 15 minutes in three, two and one patients respectively. The mean value of C_{max} in group 2 (bupivacaine + adrenaline) was 1.69 (0.35) µg/ml after the first injection. T_{max} occurred at 5, 10, 15 and 30 minutes in one, two, two and one patients respectively. After the second set of injections in group 2 C_{max} was 1.99 (0.34) µg/ml. T_{max} occurred at 5, 10, 15, and 30 minutes in two, one, one, and two patients respectively. The results of C_{max} from group 1 and the first set of injections in group 2 were not statistically different ($p > 0.05$), indicating that the use of adrenaline-containing solutions did not reliably slow absorption. The plasma concentrations of bupivacaine had not returned to zero after 6 hours in group 2, the time when the second set of injections was performed. In addition, the area under the mean concentration time curve increased by 44% in group 2 after the second set of injections. These two factors indicate accumulation of bupivacaine. Eight patients had serum concentrations of AAG above the reference range (Table 13.5), but these high concentrations did not correlate with high measured concentrations of total bupivacaine ($p > 0.05$). The patient who was studied twice had similar plasma concentrations of bupivacaine on each occasion.

Discussion

There has been one other short report of plasma concentrations of bupivacaine after intercostal blocks following liver transplantation in 3 patients (Goldberg et al 1987). This study used smaller total doses of 50-100mg making comparison of data difficult but Cmax occurred at similar times to our data at 5 mins, the first sampling time.

High plasma concentrations of local anaesthetic drugs may be a problem with intercostal blocks (Moore et al 1976; Rothstein et al 1986) owing to the large total volumes of drug solution required for the multiple injections into a highly vascular area. In patients with advanced liver disease the chest wall may have unusually large venous vessels due to portosystemic anastomoses. These collateral vessels might alter the speed of drug absorption after intercostal injection.

The mean concentrations of bupivacaine were within similar ranges to those reported in other series (Moore et al 1976; Rothstein et al 1986; Johnson et al 1987). There was no statistical difference between Cmax for the two groups with and without adrenaline. In group 1 the fact that Cmax occurred at 5 minutes in 2 patients without adrenaline suggests that Cmax may have been missed in some of these patients. Following reports of Cmax occurring early (Johnson et al 1987), an additional

sample was collected at 2.5 minutes in group II. No Cmax values were seen at 2.5 minutes in group 2. Tmax was variable between patients in both groups, but these cannot be reliably compared owing to the spacing of sampling times and the relatively small numbers of patients studied. The addition of adrenaline in the bupivacaine solution did not consistently increase the time taken to reach Cmax; this is in disagreement with other studies measuring arterial concentrations of bupivacaine after intercostal injection (Johnson et al 1987). The abnormal vasculature present in patients with liver disease may not vasoconstrict normally in the presence of injected adrenaline. In addition, the size alone of the collateral vessels may not be important. Studies in children with extensive collateral vessel formation, secondary to coarctation of the aorta, have demonstrated that absorption of bupivacaine is no different compared with children with other forms of congenital heart disease, without collateral vessel formation (Rothstein et al 1986).

No adverse reactions attributable to bupivacaine were seen in these patients despite plasma levels of bupivacaine within the putative toxic range in 6 patients (2 in group 1, 4 in group 2 following both sets of injections). This may reflect an inaccuracy of the reported toxic threshold of 2-4 µg/ml (Fitzgibbons, Moore and Balfour 1981; Tucker 1986) for bupivacaine.

The reported toxic values have been derived from studies using short intravenous infusions of bupivacaine to obtain steady state concentrations; however, differences in the analytical method, sampling sites and infusion regimen used in each of these studies make interpretation of these values complicated (Tucker and Mather 1979). Alternatively, the lack of adverse side-effects may be due to the protective effects of residual benzodiazepine sedation, which had been administered prior to tracheal extubation (DeJong and Heavner 1971). All patients in the study were rousable but had background sedation and analgesia, making precise neurological assessment impossible. In addition, the total bupivacaine concentrations measured in our study may not reflect the free, nonprotein - bound concentration of the drug which is thought to cause CNS side-effects (Denson, Myers et al 1984).

Bupivacaine is extensively bound to AAG (Denson, Coyle et al 1984), an acute phase reactant whose levels were increased in these and other patients following liver transplantation, owing to acute surgical stress and liver disease (Chapter 6). In the presence of elevated concentrations of AAG high total concentrations of bupivacaine would be measured but toxicity would not occur, as the free concentration would be normal. The concentrations of AAG were above the reference range (0.5-1.0 g/l) in 7 of the patients in this study but did

not correspond to those with increased total bupivacaine concentrations. Unfortunately, it was not possible to measure free bupivacaine concentrations nor the differing subtypes of AAG (Serbource-Goguel et al 1983; Serbource-Goguel et al 1986) and their differing effects (if any) on drug binding. The relatively normal albumin and total protein concentrations reflect aggressive treatment of hypoalbuminaemia with the infusion of albumin-containing solutions in the perioperative period.

Other factors may also have contributed to the high plasma concentrations of bupivacaine. Uptake of bupivacaine by the lungs is significant (Rothstein et al 1983) and may be competitively inhibited by drugs such as propranolol (Rothstein and Pitt 1983). Three patients had been receiving long term propranolol for control of portal hypertension before their liver transplant. However, these three patients did not develop consistently higher bupivacaine concentrations than the other patients studied. The presence of functional intrapulmonary shunting in patients with liver disease (Williams et al 1979) may also increase the availability of the drug to the systemic circulation. This has been shown experimentally, in animals, using lignocaine (Bokesh et al 1987). The potential importance of these mechanisms was not investigated in this study.

Extrapolation of these results to other patients with liver disease requires caution, since differences in the mechanisms of liver injury may alter the liver's capacity to eliminate bupivacaine. However, the results suggest that caution may be necessary in this group of patients when intercostal blocks are performed. Some patients will achieve potentially toxic levels of bupivacaine a variable time after performing the intercostal nerve blocks. Although clinical evidence of toxicity has not been seen, the recommended maximum dosage of 2mg/kg should not be exceeded in these patients. The use of adrenaline-containing solutions did not consistently reduce the speed of absorption nor the maximum concentration of bupivacaine. Furthermore, bupivacaine accumulation after repeated intercostal nerve blocks within 6-8 hours will occur in some patients following liver transplantation and possibly others with hepatic dysfunction.

CHAPTER 14

CONCLUSIONS ABOUT SEDATION AND ANALGESIA AFTER LIVER TRANSPLANTATION

The liver is central to drug metabolism and when hepatic injury occurs, alterations in the elimination of drugs are observed. In addition, poorly understood changes in the CNS receptors also occur, making the patient sensitive to sedatives and analgesics. It is therefore not surprising that a considerable amount of this thesis is devoted to the problems of excessive sedation, its mechanisms and how it may be avoided. However, the importance of the patients' need for opioids for adequate pain relief, respiratory depression and antitussive effects and sedative drugs to allay anxiety after liver transplantation has been discussed in Chapter 7.

Many of the studies in this section of this thesis have illustrated the importance of the liver in the elimination of sedatives and analgesics. The studies after liver transplantation, showing significant alterations in pharmacokinetic variables, generally illustrated delayed elimination. Three studies were performed during the anhepatic period and these demonstrated the absolute need for the liver to metabolise morphine (Chapter 11) and the presence of

extrahepatic sites able to metabolise midazolam (Chapter 8) and propofol (Chapter 10). Although the latter two studies both demonstrated extrahepatic metabolism, further increases in metabolic activity were seen when the donor liver was revascularised. The anatomical location of extrahepatic metabolic sites remains to be fully elucidated. The lungs have been suggested as a site of metabolism for many drugs, including propofol. Many of the studies have been performed in whole experimental animals or humans and have inferred results based on plasma sampling. The study in Chapter 10 did not confirm the suggestion of pulmonary metabolism made in some of these studies. The relative importance of the gastrointestinal tract, muscles, kidneys and other organs as sites for drug metabolism remains to be evaluated.

The original drugs used for sedation and analgesia were morphine and diazepam; if a muscle relaxant was required then pancuronium or curare was administered. These were given by intravenous bolus injection, primarily because only these "long acting" drugs were available and there was little need to administer them using continuous intravenous infusions. In the late 1970s "short acting" induction agents (Althesin and Etomidate) became available for use during anaesthesia. These were soon investigated as agents to be given by prolonged continuous intravenous infusion to the critically ill,

producing a controllable depth of sedation from which patients would rapidly awake when they were discontinued. A short acting, predictable analgesic, sedative or muscle relaxant is particularly attractive in this group of patients. Although both of the original drugs have now been withdrawn for this purpose, other drugs with a similar reported duration of action, including chlormethiazole, midazolam, alfentanil, and propofol, have been investigated to varying degrees in this thesis.

Infusion of these newer drugs, as well as some of the more established ones such as morphine, has gained widespread acceptance in all groups of critically ill patients, which might indicate improved efficacy compared with bolus administration, but little scientific evidence is forthcoming to support this view. Although early uncontrolled studies with infusions of opioids, for example that by Fry (1979), suggested improved analgesia, this has not been confirmed when placebo controlled, blind, randomised trials have been performed (Marshall et al 1985; Owen et al 1989). It has been argued that all of these studies occurred in a research environment and generated an interest in analgesia such that intramuscular injections, or other forms of pain relief, will be administered more frequently than would otherwise be the case. Whilst this may apply to a busy, general surgical ward it should not

occur in a well staffed intensive care unit with a high nurse/patient ratio. One of the reasons for the failure of infusions to provide superior analgesia may be the rapid development of tolerance to opiates (McQuay, Bullingham and Moore 1981; Schafer et al 1983; Marshall et al 1985), a feature demonstrated also with midazolam (Chapter 8). In uncomplicated, postoperative patients, not requiring intensive care, pain decreases as this phenomenon develops. Patients after liver transplantation have severe pain from their Mercedes incision which requires excellent pain relief for several days to facilitate weaning from artificial ventilation. There is little doubt that, if opiates are being infused, increasing the rate of infusion will achieve analgesia, and in appropriate circumstances increasing the rate of infusion of sedative or neuromuscular blocking drugs will achieve similar results. The simplicity of administering sedative drugs by continuous infusion and the desire to keep patients comfortable may lead to the patient's attendant inadvertently administering excessive sedative and analgesic drugs. Problems with continuous infusions of these drugs have arisen when they are discontinued and their effects do not end as expected. Prolonged sedation of several days' duration has been reported with midazolam (Chapter 8) and subsequently chlormethiazole (Chapter 10). Similar unexpected prolongation of effect has been described in one patient following an infusion

of alfentanil (Yate et al 1986) and in several patients with renal failure after infusions of vecuronium (Griffiths, Hunter and Jones 1984). The prolonged duration of effect of the drugs may not be recognised and has misled clinicians into thinking that cerebral impairment has occurred due to the original illness. This may result in unnecessary investigations such as cranial computerised tomography and inappropriately influence major management decisions. Furthermore, unnecessary excessive sedation may result in other difficulties, such as those discussed in Chapter 7.

Why do some patients respond to drugs in an unexpected manner? Much of the early work on the pharmacokinetics and pharmacodynamics of drugs is performed on healthy experimental animals, volunteers and ASA class 1 or 2 patients. This thesis has attempted to resolve some of the problems encountered in clinical practice by describing pharmacokinetic and pharmacodynamic studies during periods of acute illness. Furthermore, it attempts to identify some of the effects of acute organ support (such as CVVHD) on drug action. Hepatocellular function also changes in the postoperative period, and although in the majority of patients continued improvement is seen, in some deterioration due to sepsis and rejection will also be experienced. An additional factor is the changes in both portal venous and hepatic arterial blood flow, not only as a result of anaesthesia

and surgery (Gelman et al 1976) but also because of subsequent episodes of sepsis and surgery. The effects of any of these events on the denervated, human hepatic artery and portal vein are unknown. Certainly, as hepatocellular function and blood supply to the liver change, so alterations in drug elimination can be expected. This is so even with the newer drugs which have been thought to have more predictable pharmacokinetics than the older agents. Marked changes in the pharmacokinetic variables with both nalbuphine and alfentanil are reported in Chapter 12. Changes in hepatic blood flow and hepatocellular function may not always correlate with alterations in metabolic activity (MacNab et al 1986) and the possibility of small molecular weight substances interfering with drug metabolism, particularly in renal failure, has been raised (M.Tarbitt Personal Communication).

Pharmacogenetic abnormalities might also explain some of the difficulties in this group of patients. Six percent of the population have been demonstrated to be slow metabolisers of midazolam (Dundee et al 1986). It is interesting to speculate about the patient presented in Chapter 8, who during the anhepatic period of liver transplantation initially did not metabolise midazolam but did after revascularisation of the donor liver. Were her extrahepatic sites of benzodiazepine metabolism similarly affected? Liver transplantation can reverse

genetically acquired enzyme defects and this may have been an example of this. In one other patient a low plasma concentration of pseudocholinesterase, before liver transplantation, associated with apnoea after suxamethonium, became normal afterwards. In both of these patients an improvement in their ability to metabolise drugs was seen, but other patients may experience the reverse. The importance of pharmacogenetic changes does not lie during and immediately after anaesthesia (since termination of drug effect at this time is usually due to redistribution), but when the drug has been administered for a longer period of time. In these circumstances, a significant prolonged effect may be expected, since the drug is no longer redistribution-limited but is now dependent upon metabolism and excretion.

What is the answer to the effects of prolonged duration of action of sedative and analgesic drugs in patients after liver transplantation? Specific antagonists now exist for opiates (naloxone) and benzodiazepines (flumazenil). They may be given by bolus injection but because of their short duration of action, they may need to be administered by repeated bolus injection or continuous intravenous infusion (Chapter 9). Both naloxone and flumazenil are expensive and infusions of both drugs may be costly. Although they may reverse the prolonged effects of analgesics and sedatives their routine

use in this group of patients might indicate and encourage unnecessary sedation. One way to prevent oversedation whilst ensuring adequate patient comfort is to monitor and record the effect of the drug and alter the dose accordingly. This is done routinely for many other drugs that have easily defined endpoints, such as vasoactive drugs, but is rarely performed for sedatives and analgesics. A simple but effective scale, developed during the period of this thesis, has proved invaluable in improving patient care. A further method, used particularly after liver transplantation, is to recognise the need for analgesia or sedation and give an appropriate drug by bolus injection (the drugs most commonly used for these purposes are midazolam and morphine, whose elimination has been evaluated in detail in Chapters 8 and 11) to produce that effect. The result is assessed and when the effect of the drug is wearing off, a repeat bolus dose is given and this procedure repeated several more times. Only if the time interval between the doses is short is an infusion started. If an infusion is necessary, then once it has been started, unless it is obvious the patient is not excessively sedated, it should be stopped or the dose drastically reduced each day, and the patient allowed to recover, to ensure accumulation is not occurring. Should the infusion require restarting, the need to give the drug at the same rate should be questioned. Used in this way the need for the drug and its method of administration are

assessed. This method of sedation and analgesia minimises the risk of overdose and accumulation but has the disadvantage that in some patients unwanted effects may occur. Should the effect of the drug wear off unexpectedly or before a further dose can be given, sudden agitation, patient discomfort, cardiac instability and high airway pressures may develop. This method was recently tested by a physician working on the intensive care unit who managed to achieve several hours of sedation with a small, single bolus dose of propofol. As the patient emerged from the sedative effects of propofol, reassurance was given and no further anxiolytic was needed. Sedating this patient for a brief period appeared to break a vicious cycle of anxiety, producing restlessness, leading to more discomfort and so more anxiety.

A further option is to produce drugs that do not accumulate. Propofol is a drug currently under investigation in this field. Continuous infusion of propofol in the critically ill is now being increasingly advocated, its short duration of action and lack of accumulation giving it many of the properties of the ideal sedative. Initial experience has shown it to be an effective and easily controlled sedative with rapid recovery on termination of infusion (Grounds et al 1987; Aitkenhead et al 1989). However, adverse cardiovascular effects have been reported both in fit patients

(Committee for the Safety of Medicines 1989) and in the critically ill (Penfold et al 1987). Briggs and his colleagues (1987) have shown that the concurrent administration of fentanyl with propofol alters propofol's pharmacokinetics and leads to an increase in its plasma concentrations. It is not known if interactions with fentanyl and perhaps other drugs will lead to difficulties with its use during prolonged infusions.

If parenterally administered sedatives cause so many difficulties should inhaled agents be investigated again? Isoflurane has recently been studied for sedating critically ill patients for a 24 hour period and shows promise as an agent for short term use (Kong, Willatts and Prys-Roberts 1989). However, when used for longer periods of time will isoflurane be found to have unrecognised difficulties, as did nitrous oxide, perhaps related to delayed elimination of fluoride ions if renal or hepatic insufficiency develops (Chapter 7)?

When there is no longer a need for artificial ventilation intercostal nerve blockade is the preferred method of analgesia in these patients, since it appears to offer better analgesia with no clinical evidence of toxicity, although the study in Chapter 13 showed plasma concentrations in the putative toxic range. Perhaps in this instance the residual effects of benzodiazepines were beneficial! This final point highlights the need

for all clinicians and researchers in this field critically and continuously to appraise the action of all drugs both old and new. Many adverse effects and alterations in drug action remain to be described.

CHAPTER 15

RENAL DYSFUNCTION AND ITS PREVENTION AFTER LIVER TRANSPLANTATION

Mortality after liver transplantation is closely related to the development of renal failure and preventative measures to reduce the incidence of this complication decrease mortality (Chapter 15). Impairment of renal function may occur during the procedure or in the early postoperative period. Occasionally, haemodialysis or continuous haemofiltration with dialysis may be required. The most important causes of renal dysfunction include major blood loss occurring in the perioperative period and the hepatorenal syndrome.

Haemorrhage results in sympathetic vasoconstriction, which mainly affects the afferent glomerular arterioles, with a decrease in renal blood flow and consequent renal ischaemia. Septicaemia and the use of potentially nephrotoxic drugs, such as the cephalosporin or aminoglycoside groups of antibiotics (especially in combination with loop diuretics) and the immunosuppressant cyclosporin A (Bennett and Pulliam 1983), may also be causally implicated.

Numerous theories exist about the causes of renal

dysfunction in patients with hepatic disease (hepatorenal syndrome) and probably reflect the multiple factors producing this problem. Hormonal changes predominate in the hepatorenal syndrome. The first involves increases in aldosterone levels. Adrenal secretion of this hormone increases and since its destruction is dependent upon liver function, particularly liver blood flow, its breakdown is reduced in severe liver disease. Increases in the concentration of aldosterone result in sodium retention. The second feature is a decrease in effective plasma volume due to the redistribution of fluids from the intravascular space to the interstitial fluid compartment, including ascitic fluid. Hypovolaemia stimulates volume receptors, found in the atria and elsewhere, leading to an increase in secretion of renin and the production of angiotensin I. This enzyme is then changed by converting enzyme, found predominantly in the lung, to angiotensin II. Production of these substances leads to atrial vasoconstriction and an increased resorption of sodium and water in the distal tubule. Antidiuretic hormone levels are also increased in hepatic disease, and this, combined with the decreased filtrate delivered to the distal convoluted tubules and collecting system, leads to further water retention. Thus total body sodium increases and free water clearance decreases.

Other changes in patients with hepatic failure that

influence renal function include an increase in plasma noradrenaline levels to 2-5 times normal. This will increase further if patients develop renal failure. In addition there may be, as yet unknown, changes in endogenous renal prostaglandins and vasoactive intestinal polypeptides in hepatic failure that further alter intrarenal mechanisms of salt and water excretion (Koppel et al 1969).

There are no significant morphological changes demonstrable in the kidneys of patients with the hepatorenal syndrome. The deterioration in fluid and electrolyte state is purely functional, with the kidneys responding appropriately to various neurohumoural mechanisms. Tubular function is normal and the urine produced by these patients is usually concentrated. Koppel and his colleagues (1965) transplanted kidneys from patients with the hepatorenal syndrome into patients without hepatic dysfunction but with renal failure, and found that the transplanted kidneys recovered normal function. Urine from patients with hepatorenal failure has a sodium concentration of <20 mmol /l with no cells, sediment or protein detectable, a urine/plasma creatinine ratio of $>30:1$ and a urine osmolality of at least 100 mosm/kg greater than the plasma osmolality (Epstein 1982a). Other investigations are compared with those seen in normal and disease states in Table 15.1.

	Hepatorenal	Prerenal	Renal Failure	Normal
Urinary sodium (mmol/l)	<20	<20	70-100	1-150
Urine/plasma osmolality	>1.5	>2:1	1:1	>1.5
Casts	No	No	Yes	No

Table 15.1: Laboratory findings in hepatorenal failure, other causes of renal dysfunction and normal values.
(From Epstein 1982b, Park and Manara 1989)

Electrolyte Changes in Patients Presenting for Liver Transplantation

Martin (1986) studied 28 patients before liver transplantation and found that 48% of these patients were hypokalaemic. This may be a reflection of sodium retention, inadequate dietary intake, vomiting, prolonged diuretic therapy or the development of secondary hyperaldosteronism. Abnormalities of the plasma sodium concentration occurred in 52% of the patients. Hyponatraemia may have been due to excessive administration of fluids not containing sodium and the effects of an increased concentration of ADH. Hypernatraemia is usually caused by the incautious use of sodium-containing fluids. Phosphate was abnormal in 70% of the patients, 37% were hypocalcaemic, and hyper- or hypoglycaemia was a problem in 48%.

Assessment of Renal Function

Routine tests of renal function before and after liver transplantation include the estimation of plasma urea, creatinine and creatinine clearance. In the majority of patients, these tests will provide an adequate guide to renal function. Interpretation of these results in some patients requires caution. Plasma urea may be falsely low in patients with severe liver failure, particularly if the hepatic injury follows an acute overwhelming event, such as a viral infection, poisoning or idiosyncratic drug response. In this situation the

liver may no longer be able to break down protein and produce urea. However, if the liver failure is less acute then plasma urea may be artificially elevated as a consequence of recent gastrointestinal bleeding resulting in breakdown of blood to urea by bacteria. In cachectic patients plasma creatinine may be falsely low even in the presence of severe renal dysfunction and prolonged liver disease. These patients have a reduced muscle bulk and fail to produce creatine for the liver to break down to creatinine. Creatinine clearance will be reduced according to the degree of renal dysfunction, but continues to provide an adequate guide to renal function. Deeply jaundiced patients (plasma bilirubin $>300 \mu\text{mol/l}$) may provide further difficulties. In these patients the estimation of creatinine itself is unreliable. In one patient studied over 26 days, plasma creatinine was measured by five different methods and a five fold variation in the value of creatinine was demonstrated. Following storage at 4°C , plasma from this patient was reanalysed and the original values obtained by all methods had changed. The mechanism for this is obscure but may represent a small molecular weight substance that changes on storage and interferes with assay. The original results from this patient are shown in Figure 15.1. Since the initial observation of this phenomenon it has been observed on several other occasions.

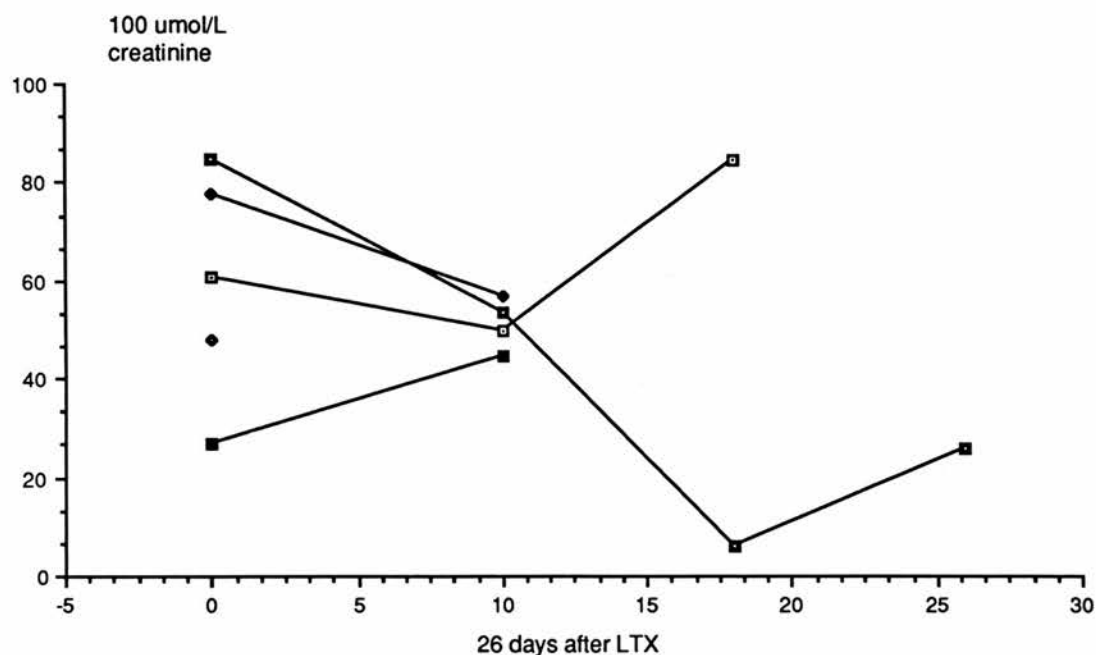


Figure 15.1: Plasma creatinine values in one patient after liver transplantation measured using 5 different assay methods: Technicon SMA2 analyser, a continuous flow end point reaction (◆), Perspective discrete analyser (■), Perspective analyser applying correction factor for elevated bilirubin (□), Traditional picrate kinetic method measured using a Beckman analyser (○), BCL kit (◇). (Measured by Dr L Culank, Consultant Chemical Pathologist, Addenbrooke's Hospital)

RENAL PROTECTION

Renal failure developing in the critically ill, jaundiced patient in the perioperative period carries a high mortality. Prevention of this complication not only reduces mortality but also is more cost-effective than its treatment. Prophylactic measures may be applicable in the circumstances surrounding liver transplantation to decrease the incidence of this complication. Dawson (1965) demonstrated that the intraoperative administration of mannitol to jaundiced patients during surgery reduced the incidence of renal failure by promoting an osmotic diuresis; from the beginning of the liver transplant programme mannitol has been infused throughout the intraoperative period. Massive haemorrhage may also occur perioperatively resulting in sympathetic vasoconstriction, mainly affecting the afferent glomerular arterioles, with a decrease in renal blood flow and consequent renal ischaemia. Dopaminergic stimulation may reverse this sympathetic vasoconstriction, maintaining or increasing renal blood flow and glomerular filtration rate (Goldberg 1972). Studies in animals and humans, when dopamine has been infused, have shown increases in cardiac output, with concomitant decreases in systemic and pulmonary vascular resistance and increases in renal blood flow (Angehn et al 1977), without significant changes in systemic blood pressure (Winso et al 1988). There is also an increase

in renal plasma flow and glomerular filtration rate. However, other effects such as intrarenal vascular changes may be responsible for the natriuresis (Carriere et al 1971; Earley and Friedler 1965) and alterations in the tubular transport of sodium have been suggested by Davis and his colleagues (1968). Studies in rats with fenoldopam suggest that these natriuretic and diuretic effects can be independent of alterations in intrarenal haemodynamic changes and a direct effect on tubular DA₁ receptors has been shown (Hegde et al 1989). Furthermore, Lightman and Forsling (1980) have demonstrated that dopamine may inhibit vasopressin release in man, although this action was not repeatable in animal experiments.

A study of the dopamine precursor, L-glutamyl dopa, to assess protection against glycerol induced renal failure in rats by Lee (1982), demonstrated an increase in creatinine clearance and less histological damage and systemic upset in the treated group than was seen in the untreated group. Used in the dose range 2-5 µg/kg/min dopamine is a potent renal dopaminergic agonist and is commonly used to treat patients with incipient renal failure (Parker et al 1981). Barnardo and his colleagues (1970) gave dopamine to 10 patients with renal failure due to cirrhosis using a dose of 1.3-3 µg/kg/min and demonstrated a significant improvement in renal function in these patients. Others have also shown that during abdominal aortic aneurysm surgery the use of low dose

dopamine can improve renal function (Salem et al 1988). Furthermore, a low dose infusion of dopamine (4µg/kg/min) has been shown in dogs to ameliorate the vasoconstrictor effects of noradrenaline on the renal artery (Schaer, Fink and Parrillo 1985). The administration of a low dose infusion of dopamine prior to and during the major haemorrhage sometimes experienced during liver transplantation, to see if a reduction in renal insufficiency could be achieved, seemed worthy of consideration. I was assisted with the data collection for this study by Dr R Polson (Registrar)

**THE PREVENTION OF RENAL IMPAIRMENT IN PATIENTS
UNDERGOING ORTHOTOPIC LIVER GRAFTING BY INFUSION OF LOW
DOSE DOPAMINE.**

Anaesthesia (1987) 42:15-19

Patients and Methods

In the 18 month period from 1st May 1983 until 31st October 1984, 34 patients were treated by orthotopic liver transplantation. One patient with primary hyperoxaluria and renal failure, who had a combined liver and repeat kidney graft operation, was treated electively with haemodialysis both before and after operation and is therefore excluded from further analysis. All patients received 10% mannitol 1g/kg during the procedure and all were given benzylpenicillin, cefoxitin and tobramycin during the

operation and for 48 hours postoperatively. For immunosuppression, prednisolone and azathioprine were used; oral cyclosporin A was introduced in the second postoperative week in order to avoid the renal and pulmonary toxicity associated with intravenous administration immediately after operation (Powell-Jackson et al 1984).

Nineteen patients (21 transplant operations) received a low dose dopamine infusion of 2 $\mu\text{g/kg/min}$, begun with the induction of anaesthesia and continued for 48 hours postoperatively (Group 1), while 15 patients (15 transplant operations) did not (Group II). A patient who required retransplantation for chronic rejection six months after her first transplant operation was treated with dopamine prophylactically only during her second operation and so is included in both groups. During this period there was no formal policy about the use of prophylactic dopamine, the decision whether or not to use it being made by the consultant anaesthetist involved.

The perioperative details of these two groups were compared, as was the incidence of renal impairment defined as oliguria (less than 0.5 ml/kg/hr urine output) in the presence of an adequate central venous or pulmonary capillary wedge pressure and a urine/plasma osmolality ratio of 1.1 : 1.0 or less (Lee 1979), or

acute renal failure requiring haemodialysis. In accordance with conventional management a dopaminergic dose of dopamine was begun immediately a patient in Group II developed renal impairment.

To determine whether partial cardiopulmonary bypass support had a beneficial effect on renal function, the results for the five patients in the dopamine treated group in whom veno-arterial bypass (Calne et al 1984) was used and for the six patients in the untreated group in whom veno-venous bypass (Shaw et al 1984) was used, were compared with the remaining patients in their respective groups. Similarly, since younger patients have better survival rates than older patients after liver transplantation (Williams et al 1985), the renal function of those aged 21 years or under was compared with that of the older patient within each treatment group.

Six pairs of patients were matched for age, sex and diagnosis and as closely as possible for preoperative weight, plasma creatinine concentration and intraoperative blood loss and degree of hypotension. One of each pair was receiving low dose dopamine. The one patient who required retransplantation for chronic rejection six months after her first operation was included as the seventh "pair".

Statistical analysis was by Student's t-test for unpaired data, Mann-Whitney U test and Fisher's test of exact probability where appropriate.

Results

The two groups of patients were similar with respect to age, sex, diagnoses, preoperative plasma creatinine, and operative blood loss (Table 15.2).

In Group 1, 19 patients received low dose dopamine prophylactically and only 2 (9.5%) of the 21 transplant operations were complicated by acute renal failure. A 13 year old female who had compromised renal function before operation, with a plasma creatinine concentration of 150 $\mu\text{mol/l}$, required haemofiltration from 6 days postoperatively and haemodialysis from 13 days, while a second patient (a 46 year old man) required haemofiltration from two days and haemodialysis from ten days postoperatively.

In contrast, of the 15 patients (15 transplant operations) in Group II not electively treated with dopamine, ten patients (67%) developed renal impairment, a statistically highly significant difference ($p = 0.001$). In three patients this occurred during the operation; one patient subsequently required haemodialysis from the sixth postoperative day; six patients required dopamine within the first 24 hours

after operation and three of these required haemodialysis within the first postoperative week, while the remaining patient started dopamine during the second postoperative day.

The incidence of renal impairment in patients in whom bypass support was used was not significantly different from the remaining patients in their respective groups. Likewise, no difference was found when the results within the two treatment groups were analysed with respect to age.

When the results for the paired patients were compared it was found that the volume of urine produced on the first postoperative day and the creatinine clearance in the period 24-48 hours after operation were significantly better in those patients who received prophylactic dopamine than in those who did not ($p < 0.05$, Table 15.3). There was no significant difference in preoperative renal function, operative blood loss and lowest systolic blood pressure between the two groups.

	Group 1	Group 2
	Prophylactic Dopamine	No Prophylactic Dopamine
Number of transplant operations	21	15
Number of Patients	19(7M:12F)	15(6M:9F)
Age (years)		
Mean (SEM)	29.7 (4.3)	34.5 (4.3)
Range	2-58	2-57
Diagnosis		
Biliary atresia	3	1
Inborn errors of metabolism	1	1
End stage liver disease		
Primary biliary cirrhosis	5	4
Chronic active hepatitis	3	2
Others	6	3
Malignant liver disease	1	4
Operative Blood Loss (litres)		
Mean (SEM)	9.5 (2.9)	7.3 (1.7)
Range	0.3-54.0	1.0-22.2
Preoperative plasma creatinine concentration ($\mu\text{mol/litre}$)		
Mean (SEM)	75.9 (6.6)	79.0 (4.8)
Range	45-150	46-102
Outcome		
Renal Impairment at 2 weeks	2/21 (9.5%)	10/15 (67%)
Renal Failure at 2 weeks	2/21 (9.5%)	4/15 (27%)

Table 15.2: Patient information and results in 34 consecutive patients undergoing orthotopic liver transplantation from 1 May 1983 - 31 October 1984. One group received $2\mu\text{g/kg/min}$ of dopamine prophylactically before and after liver transplantation, the other group did not.

PAIRS

	1		2		3		4		5		6		7	
Patient number	166	164	165	145	159	150	157	124	170	147	162	117	148	148
Age (years)/sex	46F	46F	50F	48F	2M	2M	17F	17F	13F	10F	52M	47M	11F	
Diagnosis	PBC		PBC		BA		CAH		Hepatoma		AC		R SAH	
Weight(kg)	50	44	58	60	13.8	12.0	52	50	35	36	80	81	40	36
Pre-op plasma creatinine(μ mol/litre)	91	64	70	69	-	-	61	119	49	58	97	108	46	107
Blood loss(litres)	3.8	6.0	7.9	5.0	0.7	2.3	7.4	4.1	0.3	3.9	16.6	7.9	11.3	3.9
Lowest systolic BP(mmHg)	80	90	100	80-85	90	75-80	95	85	70	80	65-70	90	80	90
Urine output (ml)														
0-24 hours	1420	1700	2240	490	720	181	1010	550	1530	940	2040	630	1190	370
24-48 hours	2710	1730	2020	170	440	550	1850	2400	1880	780	4480	150	1260	740
Creatinine clearance(ml/minute)														
0-24 hours	74	50	70	9	15	61	51	35	108	90	74	13	30	8
24-48 hours	64	39	77	1	11	12	103	44	94	52	129	1	23	10

Table 15.3: Renal function in paired patients. The first patient in each pair was treated with prophylactic low dose dopamine.

Discussion

This study suggests that the prophylactic administration of dopamine, begun prior to the onset of surgery, decreases the incidence of renal impairment postoperatively in patients undergoing liver transplantation. Furthermore, although the numbers are small, renal failure requiring haemodialysis or continuous arteriovenous haemofiltration occurred less often and much later when prophylactic dopamine was given.

The problems associated with results obtained from a retrospective study are well known. The dramatic decrease in morbidity and mortality associated with the continuing use of prophylactic dopamine has been maintained since the end of the study period and for ethical reasons a prospective study in these patients could not be considered. The inclusion in this study of a matched pair group overcame some of the difficulties associated with a retrospective study and tends to reinforce the conclusions drawn from the findings of the larger, unmatched group. The use of bypass, to decompress the portal circulation and to maintain systemic blood pressure and renal perfusion, made no difference to the frequency with which renal impairment occurred (Shaw et al 1984). Also, the patients' age did not appear to alter the incidence of renal impairment, in contrast to its effect on overall mortality in which

the older patients did less well (Williams et al 1985).

The introduction of cyclosporin A has improved immunosuppression following organ transplantation (Calne et al 1979). However, its use in the early postoperative period following liver transplantation is limited by its nephrotoxicity. This necessitates the use of azathioprine, with the hazards of marrow suppression, and of high dose steroid therapy, with the disadvantages of an increased risk of infection and difficulty in the diagnosis of infection and adverse effects on carbohydrate metabolism which make parenteral nutrition difficult. Preliminary studies have shown that intravenous cyclosporin A results in a marked decrease in renal blood flow (P R Powell-Jackson, personal communication) and it may be that simultaneous low dose dopamine infusion would prevent, or at least lessen, this decrease and thus reduce the toxicity. Shortly after this study was completed a patient who was treated immediately after operation with cyclosporin A, given through a central venous line, developed severe pulmonary toxicity, but the anticipated nephrotoxicity did not develop, possibly owing to the continued administration of dopamine. Since this study was performed and low dose dopamine became part of the routine management of these patients, earlier postoperative use of this agent has been possible. It remains to be determined whether initially avoiding severe

cyclosporin A nephrotoxicity reduces the chances of long term kidney damage.

Despite the use of dopamine in this study 10% of patients in the treated group still developed renal failure. Other agents need to be evaluated to see if this figure can be decreased. Dopexamine hydrochloride is a new synthetic catecholamine. Like dopamine, dopexamine stimulates dopaminergic receptors of the DA₁ and DA₂ subtypes, though there is considerably less affinity for the DA₂ receptor than is seen with dopamine. Unlike dopamine, dopexamine has an action at the β_2 receptor, stimulation of which also results in an increase in renal blood flow due to a direct effect on the renal vasculature (Brown et al 1985; Smith and O'Conner 1988). There is no activity at alpha adrenoreceptors, and only minimal β_1 adrenoreceptor activity (Brown et al 1985). There is therefore reason to believe that dopexamine will have similar renal effects to dopamine, and its β_2 agonist activity and lack of alpha effects suggest that it may be even more effective clinically, although when administered to human volunteers it was shown to increase renal blood flow but not to the same extent as dopamine (Mousdale et al 1988). In addition to its renal effects, dopexamine also has a mild positive inotropic activity and may be of particular use when deterioration in renal function follows a decrease in cardiac output (such as that associated

with acute or chronic heart failure) which then leads to a decrease in renal blood flow and consequently renal arteriolar vasoconstriction. Both Leier (1988) and Tan (1987) and their colleagues demonstrated the benefits of dopexamine in this situation. Beta adrenergic stimulation resulted in an increase in cardiac output, a decrease in systemic vascular resistance, and an increase in urine volume and sodium excretion was due to dopaminergic stimulation. A further, unpublished study comparing dobutamine with dopexamine has shown that the increase in renal function with dopexamine is not entirely attributable to an increase in cardiac output but is due to its specific effects on the renal vasculature.

These advantages and encouraging initial clinical experience with dopexamine in the management of oliguria (Dawson et al 1985; Bodenham and Park 1988) led to a comparison of dopexamine with dopamine for renal protection in a further study in the perioperative period of liver transplantation. I was assisted with the data collection by Dr P A Gray (Registrar).

**A COMPARISON OF LOW DOSE DOPEXAMINE AND DOPAMINE
INFUSIONS IN PREVENTION OF RENAL IMPAIRMENT IN PATIENTS
UNDERGOING ORTHOTOPIC LIVER TRANSPLANTATION.**

Anaesthesia (1991) (In Press)

Patients and Methods

The trial was an open study involving two groups, each of twelve patients, undergoing orthotopic liver transplantation. After induction of anaesthesia a continuous intravenous infusion of dopexamine at a rate of 2 $\mu\text{g/kg/min}$ was started in the first group. If the heart rate did not increase by more than 20 beats per minute on the initial dose then the infusion was increased to 3 $\mu\text{g/kg/min}$. If an increase in heart rate was seen then the rate was reduced to 2 $\mu\text{g/kg/min}$. However, if on starting the infusion the heart rate increased by greater than 20 beats per minute, 1 $\mu\text{g/kg/min}$ was used as the infusion rate. Similarly, systolic blood pressure was not allowed to increase or decrease by more than 20 mmHg from baseline value. The infusion of dopexamine was continued for 48 hours after the end of surgery or until renal protection was no longer required.

Each patient was matched for age, preoperative creatinine clearance, blood loss and, as far as possible, diagnosis with another patient requiring liver transplantation who received an infusion of dopamine (2 $\mu\text{g/kg/min}$) from induction of anaesthesia and also continued

for 48 hours after the end of surgery. Mannitol 1 g /kg/6hr was infused throughout the operation. For immunosuppression, prednisolone was administered from the time of surgery and cyclosporin A was introduced two days postoperatively, after the study was finished and if renal function was adequate.

In order to compare the efficacy of dopexamine and dopamine, urine output was measured hourly for 48 hours postoperatively. The urine/plasma osmolality ratio was measured preoperatively, on admission to the intensive care unit and on days one and two postoperatively. Creatinine clearance rates were also measured preoperatively and over the first and second 24 hour periods postoperatively. Patients were observed for seven days postoperatively to record the incidence of renal impairment or failure. The same criteria were used, as described earlier, for the recognition of these complications, except that renal failure was defined as the need for continuous haemofiltration with dialysis. Since the effects of the two drugs on the splanchnic, peripheral and other circulations may differ because of their different adrenoreceptor specificity, a note was made of the lowest systolic arterial blood pressure, blood loss and its replacement. Frusemide is usually administered immediately prior to weaning from artificial ventilation (Chapter 5). It is not given if the patient is polyuric at this time or if the patient

is not weaned from artificial ventilation during the study. Diuretic usage which may therefore have affected urine volumes was also recorded.

Statistical methods used to assess the effects of each drug are described below.

Results

The demographic information for the two patient groups is shown in Table 15.4. The second patient, who was female, was inadvertently matched with a male patient. There were no statistically significant differences in age, weight, operative blood loss or its replacement or the lowest systolic blood pressure observed in either groups (Mann-Whitney U test). Table 15.5 shows the results of the measurements that were made in these patients. Preoperative urine/plasma osmolality ratios (prior to drug administration) were significantly greater in the dopexamine group than in the dopamine group ($p=0.028$). There were, however, no other significant differences between treatment groups during the infusion period (Freidman test, Mann-Whitney U-test) for creatinine clearance values or urine volumes produced in the first and second 24 hour periods (either between the first and second 24 hour periods in each patient [Student's t test for paired data] or between treatment groups [Student's t test for unpaired data]).

		Dopexamine group	Dopamine group
Age (years)	Mean	43.7	48.5
	Range	24 - 56	24 - 58
Sex	Male	1	2
	Female	11	10
Weight (kg)	Mean	58.4	58.1
	Range	45 - 91.2	42.2 - 95.0
Blood Loss(l)	Mean	5.1	6.7
	Range	1.5 - 15	1.4 - 12
Blood Replacement(l)	Mean	5.3	7.4
	Range	1.5 - 14.7	1.0 - 16.5
Lowest Systolic Blood Pressure (mmHg)	Mean	69.2	70.0
	Range	0 - 100	0 - 100
Diagnosis			
Primary biliary cirrhosis		6	7
Chronic rejection		2	3
Neoplasm		3	0
Cryptogenic cirrhosis		1	1
Halothane hepatitis		0	1

Table 15.4. Information for the two patient groups.

	Dopexamine group	Dopamine group
Urine output(l)	n=11	n=12
0-24 hrs	2.35 (0.45)	2.03 (0.80)
25-48 hrs	2.21 (1.09)	2.21 (0.60)
Urine plasma osmolality ratio	n=10	n=6
Preoperative	2.1 (0.25)	1.5 (0.14)
Postoperative	1.4 (0.09)	1.3 (0.10)
Day 1 after surgery	2.0 (0.17)	1.6 (0.21)
Day 2 after surgery	2.3 (0.13)	2.1 (0.33)
Creatinine clearance (ml /min)	n=9	n=7
Preoperative	61.3 (8.0)	51.7 (4.7)
0-24 hours	57.6 (8.7)	58.6 (10.0)
24-48 hours	72.3 (13.5)	55.6 (14.4)
Renal dysfunction		
renal impairment	3	8
renal failure	1	3

Table 15.5. Urine volumes [mean (SD)] for the first and second 24 hour periods, urine/plasma osmolality ratios [mean (SEM)], creatinine clearance values [mean(SEM)] and incidence of renal dysfunction for the 2 groups of patients receiving renal protection.

Five patients in the dopexamine group and nine patients in the dopamine group received frusemide, but this difference was of doubtful statistical significance ($p=0.1$, Fishers Exact test). The mean amount of frusemide administered was 32.9mg in the group receiving dopexamine and 43.3mg in the group receiving dopamine, which approached statistical significance ($p=0.078$ Mann Whitney U Test).

The incidence of both renal impairment and failure was greater in those patients who received dopamine than those who received dopexamine. However, these differences were not statistically significant (Fisher's exact test) but this may also reflect the small numbers of patients studied.

Discussion

In this study, dopexamine has been shown to be as effective as dopamine for renal protection in patients undergoing orthotopic liver transplantation. The incidence of renal impairment and failure was greater in the dopamine group than in the dopexamine group, but this did not achieve statistical significance. The lack of statistically significant difference in this parameter and also in the others may have been due to the small groups of patients.

The lack of alpha agonist properties shown by dopexamine

(Brown et al 1985) may be a potential advantage compared with dopamine. Renal vasoconstriction and a decrease in renal blood flow is seen with alpha stimulation in some circumstances. Dopamine has alpha agonist properties at doses in excess of 10µg/kg/min and may in some patients have such an effect even at low doses (Bodenham and Park 1988). Furthermore, dopamine should be administered through a centrally placed venous catheter to avoid the risk of extravasation into the superficial tissues. Should this occur, the high local concentrations of dopamine lead to intense vasoconstriction, due to alpha stimulation, and subsequent skin necrosis. Dopexamine with its lack of alpha effects does not cause vasoconstriction and so where necessary can be administered by infusion through a peripheral vein. In addition, dopexamine has the added benefit of producing generalised vasodilation, mediated through β_2 adrenoreceptors, and therefore potentially an increase in tissue perfusion in other organs, including the liver, which may be advantageous in many clinical situations, especially in the critically ill.

In the earlier study, with dopamine the incidence of both renal impairment and failure was reduced to 9.5% in patients who received dopamine compared with 67% and 27% respectively in those who did not. In this study, the incidence of both renal impairment and failure in patients receiving dopamine had increased to 66% and 25%

respectively. Even with dopexamine the incidence of renal impairment was 25%, greater than that reported in the earlier series, although renal failure occurred with a similar frequency. There are three possible reasons for this difference. In the initial study children were included and this is reflected in the age (mean, range, years) of the patients receiving dopamine (29.7, 2-58) and placebo (34.5, 2-57). Owing to the difficulties of using novel compounds in children they were specifically excluded from this study with a resultant increase in the age of the patient groups. In the group receiving dopexamine the mean (range) age was 43.7 (24-56) years and in the dopamine group it was 48.5 (24-56) years. Children tolerate the major physiological insults of this and other operations better than adults, presumably because of the lack of the degenerative disease found in the older age groups. In the intervening four years more seriously ill patients have been transplanted and are thus at greater risk of renal dysfunction. Unfortunately, the lack of severity scoring makes this difficult to substantiate scientifically. Finally, the two studies differed in their design, the first being retrospective and this one prospective. This difference might have led to under-recognition of renal impairment in the retrospective study. This argument might be supported by the similar incidence of renal failure, which is more easily recognised, in the treated groups.

The prophylactic use of a dopexamine infusion has been shown to be as effective as dopamine for renal protection in patients undergoing liver transplantation, but the need for further prospective double blind studies involving larger groups of patients is illustrated.

Despite their widespread use, little is known about catecholamine pharmacokinetics in disease states. The liver is thought to be a major site for metabolism of catecholamines (Sacca et al 1986) and in liver disease alterations in their elimination may be expected. As dopexamine is metabolised in a similar way to other catecholamines (Neale et al 1986), any alterations in plasma concentration seen with dopexamine may also occur with other catecholamines.

This next study was designed to investigate the plasma concentrations of dopexamine hydrochloride in patients undergoing orthotopic liver transplantation who were receiving low dose dopexamine infusions as part of the above study for renal protection. Dr Gray assisted with the sample collection.

**PLASMA CONCENTRATIONS OF DOPEXAMINE HYDROCHLORIDE IN
PATIENTS DURING AND AFTER ORTHOTOPIC LIVER
TRANSPLANTATION**

Patient and Methods

The trial was an open study in seven patients undergoing orthotopic liver transplantation. After induction of anaesthesia a continuous intravenous infusion of dopexamine at a rate of 2 $\mu\text{g/kg/min}$ was started through a centrally placed venous catheter. The dose was titrated in the same manner as described in the previous study. The infusion of dopexamine continued for 48 hours after the end of surgery or until renal protection was no longer required.

Blood was removed from a previously sited radial arterial line immediately prior to starting the dopexamine infusion and at 10 and 20 minutes. Sampling was not continued during the period of dissection since this would have lead to an excessive blood loss and it was assumed that a steady state would have been reached after 20 minutes (about six half-lives). Further blood samples were taken at 2, 5, 10, 20 and 40 minutes after the start of the anhepatic period and at 2, 5, 10, 20, and 40 minutes, 1, 2, 12, 24, and 48 hours after reperfusion of the donor liver. The blood was immediately put into sequestrene tubes, rapidly frozen by immersion in liquid nitrogen and stored at -20°C

until analysed for dopexamine concentration by high performance liquid chromatography (Method on File, Fisons PLC).

Results

The demographic information for the seven patients, all of whom were female, is summarised in Table 15.6. Plasma concentrations, which are shown in Figure 15.2, increased in the 20 minute dose titration phase. Sampling restarted 2 minutes into the anhepatic phase and plasma concentrations of dopexamine increased further. T_{max} occurred at the end of the anhepatic period and C_{max} (SD) was 253.54ng/ml (75.77).

When the donor liver was reperfused plasma concentrations of dopexamine decreased, reaching a steady state in one to two hours. The lowest plasma concentration of dopexamine [mean (SD)] of 105.74 ng/ml (30.23) was reached after 2 hours, a value which is less than half that seen at the end of the anhepatic period.

Discussion

The changes in plasma dopexamine concentrations seen in the anhepatic and reperfusion phases, in the presence of low blood loss and cardiovascular stability for the majority of the study period, demonstrate alterations in dopexamine elimination.

Patient number	Age (Yrs)	Dose ($\mu\text{g/kg/min}$)	Diagnosis	Blood loss (l)	Lowest Systolic BP (mmHg)
1	56	2	Retransplant for chronic rejection	3	90
2	32	2	Cryptogenic cirrhosis	15	65
3	24	1	Retransplant for chronic rejection	3.5	100
4	51	3	Cholangiocarcinoma	4.2	75
5	55	2	Hepatocellular carcinoma	2.5	0 *
6	56	2	Primary biliary cirrhosis	1.5	100
7	44	2	Primary biliary cirrhosis	3.9	85

Table 15.6: Information for the 7 patients receiving dopexamine infusion during orthotopic liver transplantation. * This patient suffered a short period of asystole at reperfusion of the liver due to hyperkalaemia which resolved with cardiac massage alone.

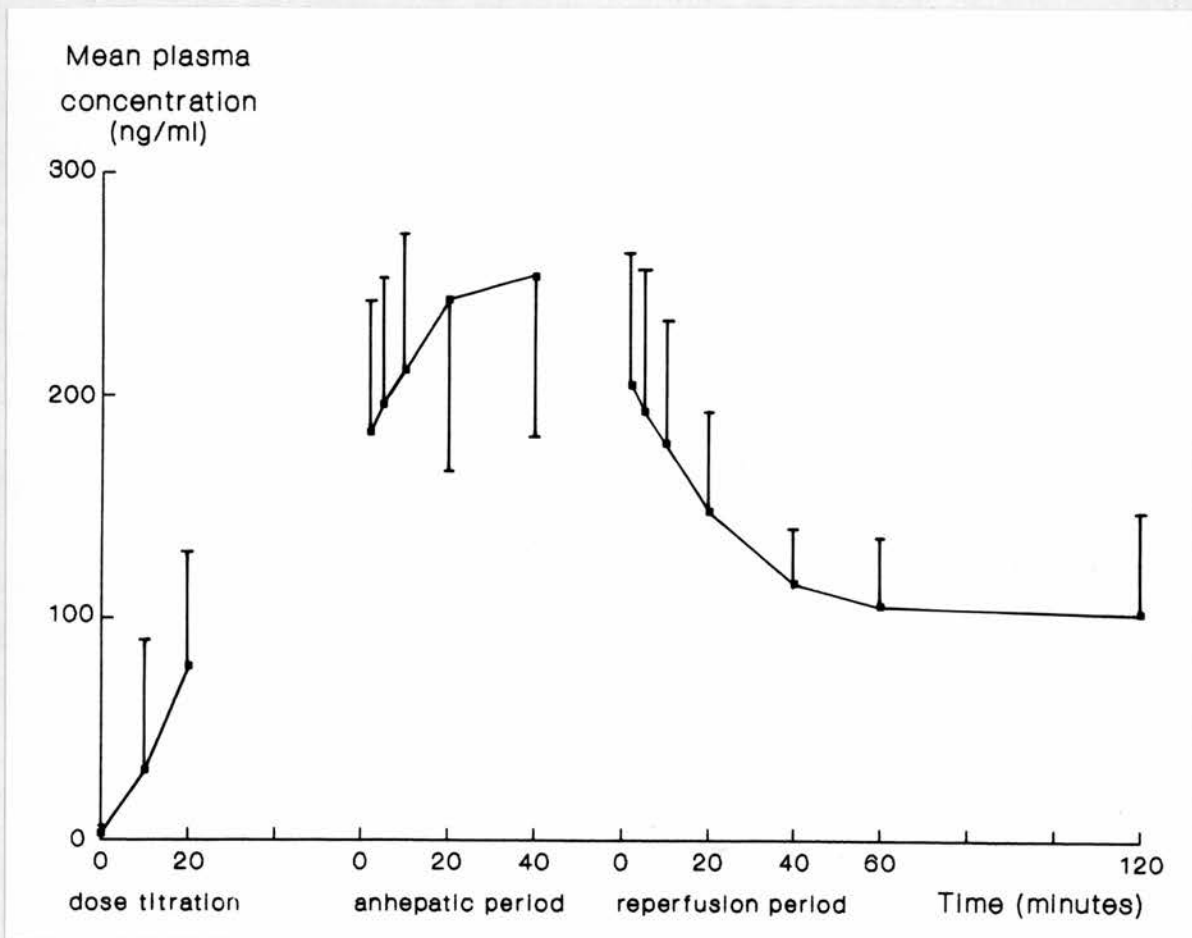


Figure 15.2: Mean (SD) plasma concentrations of dopexamine during the dose titration and anhepatic periods and for the 2 hours after revascularisation.

At the start of the anhepatic period plasma concentrations of dopexamine increase, suggesting that elimination is reduced. Plasma concentrations of dopexamine increase less rapidly as the anhepatic period progresses, suggesting that a steady state is being reached. When the liver is reperfused, plasma concentrations of dopexamine decrease as elimination increases. This suggests that the donor liver rapidly regains the capacity to metabolise dopexamine, which corresponds with the rapid recovery of metabolic capacity for midazolam and morphine previously demonstrated (Chapters 8 and 11).

Dopexamine is known to be metabolised by O-methylation and sulphation (Neale et al 1986) and is thought to be metabolised primarily in the liver. Other catecholamines including dopamine and dobutamine are thought to be metabolised in the same manner. It is likely that alterations in plasma concentrations similar to those shown with dopexamine will be observed with other catecholamines in the absence of hepatic function. In the presence of severe hepatic failure plasma catecholamine concentrations may be higher than predicted.

Although this study shows that dopexamine elimination is reduced in liver failure, plasma catecholamine concentrations are of limited value in trying to predict

a haemodynamic or pharmacodynamic end point. However, there are many peripheral effects of catecholamines such as metabolism and leucocyte function (Unpublished observation) which are not yet understood. Unnecessarily high plasma concentrations of these drugs may in these circumstances be detrimental.

Although the effects of dopaminergic and β_2 stimulation on renal function have been presented in this chapter, effects on other organs may also occur. These may include a general increase in splanchnic blood flow which may decrease the incidence of stress ulceration (MacNaughton and Wallace 1989) and improve anastomotic healing. Dopamine has been shown to increase estimated hepatic blood flow (EHBF) under many conditions including peritonitis and haemorrhagic shock (Hasselgren, Biber and Fornander 1983; Townsend et al 1987; Trachte and Lefer 1977), possibly by increasing the portal venous supply rather than hepatic artery flow (Hirsch, Ayabe and Glick 1976). The increase in EHBF is usually associated with an increase in cardiac output, though the percentage increase in EHBF is greater than the increase in cardiac output, implying some selective dilatation of the hepatic vasculature (Maestracci 1981). Dopaminergic stimulation increases portal vein blood flow. The hepatic artery also has β_2 receptors which result in an increase in flow when stimulated, although the precise location of the receptors is unclear

(Hirsch, Ayabe and Glick 1976). One patient is presented in whom the use of dopexamine may have resulted in an increase in hepatic blood flow. I was assisted with the data collection by Dr R Munglani (Registrar) and Dr P Gray.

***INCREASES IN OXYGEN CONSUMPTION DURING
ADMINISTRATION OF DOPEXAMINE IN LIVER FAILURE.***

Journal of Clinical Intensive Care 1990 1: 187-188

Patient

A 22-year-old male with α_1 -antitrypsin deficiency developed fulminant hepatic coma, precipitated by pneumococcal peritonitis and complicated by the subsequent development of hyponatraemia of 109 mmol/L. Urgent liver transplantation was considered to be the treatment of choice and shortly thereafter a donor liver became available.

Preoperatively the patient was transferred to the intensive care unit, where he was artificially ventilated and pulmonary and systemic arterial catheters were inserted to optimise his haemodynamic stability. Since this patient was oliguric (urine output <20 ml/hr), despite volume resuscitation, it was decided to use a dopaminergic agonist to improve urine output. Dopexamine was therefore infused at 1 μ g/kg/min and increased every 15 minutes to a maximum of 4 μ g/kg/min. This unusual situation of a patient in hepatic failure about to

undergo liver transplantation enabled us to study the pathophysiological effects of β_2 and dopaminergic agonism on hepatic function and shortly thereafter remove the organ for histological examination without antemortem changes. Haemodynamic variables and oxygen delivery and consumption were measured both before starting the dopexamine and at the maximum dose (Table 15.7).

With increasing dose of dopexamine there was little change of the haemodynamic parameters or oxygen delivery, but oxygen consumption doubled. Liver transplantation occurred 3 hours after this study. The histological examination of the diseased liver revealed cirrhosis with most of the right lobe being infarcted as well as smaller infarcts in the left lobe (Figure 15.3).

Discussion

Increases in oxygen consumption may be due to several reasons. Improvements in oxygen delivery, redistribution of blood flow and changes in the metabolic activity of the patient are amongst the commonest. Oxygen delivery did not change in this patient. Redistribution of blood flow is the most likely explanation for the changes seen in this patient since no changes occurred in the measured cardiovascular parameters.

Dose of Dopexamine ($\mu\text{g/Kg/min}$)	0	1	2	3	4
Mean Systemic Arterial Pressure (mmHg)	60	69	63	62	61
Right Atrial Pressure (mmHg)	10	9	8	8	8
Mean Pulmonary Artery Pressure (mmHg)	15	15	14	14	14
Pulmonary Capillary Wedge Pressure (mmHg)	15	15	15	13	13
Cardiac Index (l/min/m^2)	4.98	5.24	5.01	5.19	4.99
Systemic Vascular Resistance (dynes/sec/cm ⁵)	408	470	449	423	433
PaO ₂ (kPa)	22.2				14.6
PvO ₂ (kPa)	7.8				7
PaCO ₂ (kPa)	4.2				4.3
O ₂ Oxygen Delivery (mls/min/m^2)	1176				1176
O ₂ Consumption (mls/min/m^2)	98				196

Table 15.7: The effect of increasing dose of dopexamine on haemodynamics and oxygen consumption and delivery in a patient with fulminant liver failure.

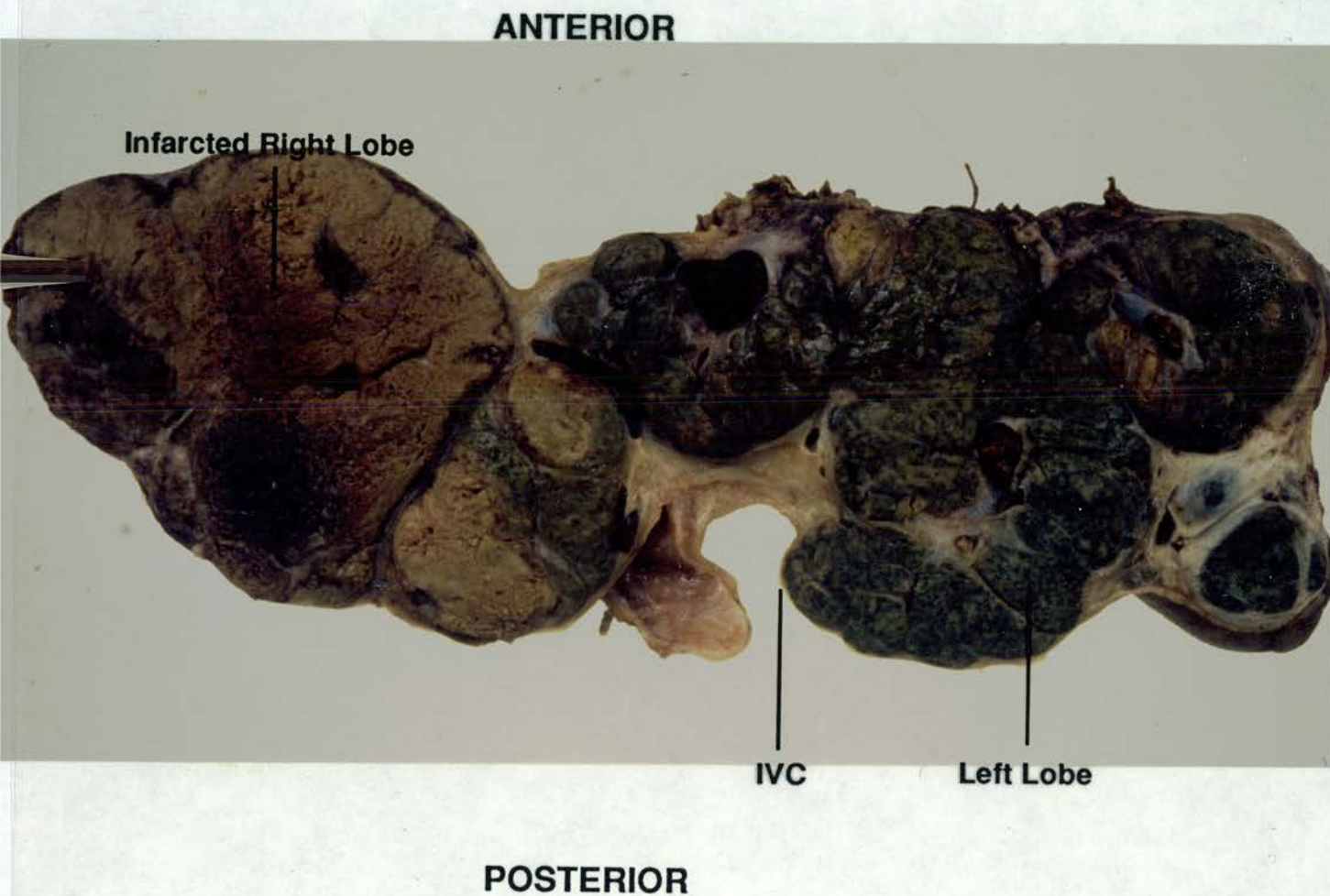


Figure 15.3: Section through diseased liver showing most of the right lobe infarcted (pale area) and smaller infarcts in the left lobe.

The increase in oxygen consumption can be attributed to a redistribution of blood flow to the splanchnic bed and, in particular, the liver, which accounts for 20% of resting oxygen consumption of the body. Dopexamine may have exerted its effect by increasing portal vein and hepatic artery blood flow. Alternatively, since cirrhotic livers have been shown to have portal vein-hepatic vein anastomoses (Strunin 1977), alterations in intrahepatic flow may have occurred with no increase in total hepatic blood flow. Either of these two possible effects might result in reperfusion of existing ischaemic areas and an increase in oxygen consumption.

Catecholamines are known to increase metabolic rate in humans, although this is a feature usually associated with doses in excess of the ones used in this patient. However, little is known about the effects of this group of drugs on metabolic activity in critically ill patients with this degree of liver failure. The practical difficulties of further investigation in this group of patients are great, but of importance, since these drugs may help provide a bridge to transplantation whilst waiting for a donor organ to become available.

POSTOPERATIVE INTRA-ABDOMINAL BLEEDING

Chronic liver disease frequently results in portal hypertension with large, abnormal blood vessels in both the skin and peritoneum. These are divided during liver transplantation and despite meticulous attention to haemostasis, torrential bleeding, may occur which can be impossible to stop intraoperatively. On rare occasions the liver, a large vascular organ, may also be inadvertently lacerated, resulting in bleeding. Should the bleeding be impossible to control then it is usual to close the patient's abdomen and return them to the Intensive Care Unit for a period of 6 to 36 hours, during which time the abdomen is allowed to tamponade. The increasing abdominal pressure will compress the bleeding points and stop the haemorrhage. Once bleeding has stopped, the patient is again taken to the operating theatre and blood clot evacuated from the abdomen. The immediate changes following decompression of the abdomen had not been reported. Both measurement and interpretation of these changes had proved difficult in the past because of the presence of anaesthetic agents and concurrent rapid blood transfusion. However, increasing familiarity with this problem allowed the opportunity to measure these haemodynamic changes in a controlled manner on four occasions in three patients

immediately before and after release of abdominal tamponade resulting from intra-abdominal bleeding. Measurements made during the release of tamponade in the first patient studied indicated that rapid blood transfusion at the time of decompression was inappropriate. Observations were, therefore, made in a more controlled manner on the three subsequent occasions, when more personnel were available to assist with frequent intensive monitoring. I was assisted during these operations by Dr Maire P Shelly and Dr A A Robinson (Registrar) and with the monitoring by Mr J W Hesford (Department of Clinical Measurements).

***THE HAEMODYNAMIC EFFECTS FOLLOWING SURGICAL
RELEASE OF RAISED INTRA-ABDOMINAL PRESSURE.***

British Journal of Anaesthesia (1987) 59; 800-805

Patient 1

The first patient was a 35 year old man who underwent orthotopic liver transplantation for hepatic failure secondary to sclerosing cholangitis. After surgery he continued to bleed from intra-abdominal sites and required massive blood transfusion; although some blood was lost from abdominal drains these functioned inadequately and he developed a tense distended abdomen. His coagulation screen was slightly abnormal in spite of infusion of fresh frozen plasma and platelet concentrate but there was no clinical evidence of a

significant coagulation disorder, such as bleeding from his nose, mouth, pharynx or the sites of venous or arterial cannulation.

Eight hours after his liver transplant operation, laparotomy was undertaken to evacuate intra-abdominal clot and to achieve haemostasis. During re-exploration, cardiovascular parameters were measured: heart rate (HR) was taken from the electrocardiogram, mean arterial pressure (MAP) was measured via an indwelling radial artery catheter and mean right atrial pressure (RAP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were measured using a pulmonary artery catheter (Edwards Laboratories) positioned immediately before surgery. Cardiac output (CO) was measured by a thermodilution technique and values were calculated for systemic (SVR) and pulmonary (PVR) vascular resistances.

On opening the peritoneal cavity, approximately six litres of blood and clot were removed. No arterial bleeding points were found to account for the haemorrhage but there was a generalised ooze from many intra-abdominal sites. Intraoperative hypotension was treated with blood transfusion; however, since calculation of systemic vascular resistance showed it to be low, methoxamine 20mg and ephedrine 30mg were administered.

The measurements obtained are shown in the Figure 16.1. Heart rate decreased immediately after decompression. There was a decrease in mean arterial pressure but little change in mean pulmonary arterial pressure. Both right atrial pressure and pulmonary capillary wedge pressures initially decreased following decompression but then increased to baseline levels. There was a prompt increase in cardiac output and pulmonary vascular resistance and a decrease in systemic vascular resistance. Following treatment with methoxamine and ephedrine, mean arterial pressure increased slightly accompanied by an increase in cardiac output but systemic vascular resistance remained low.

Patients 2 and 3

Two other patients underwent orthotopic liver transplantation for sclerosing cholangitis and continued to bleed in the postoperative period. The details of all three patients are compared in Table 16.1.

Patients 2 and 3 also required massive blood transfusion to replace blood lost from abdominal drains and intra-abdominal losses. Both underwent laparotomy for decompression of abdominal tamponade, one patient on two occasions (3a and 3b).

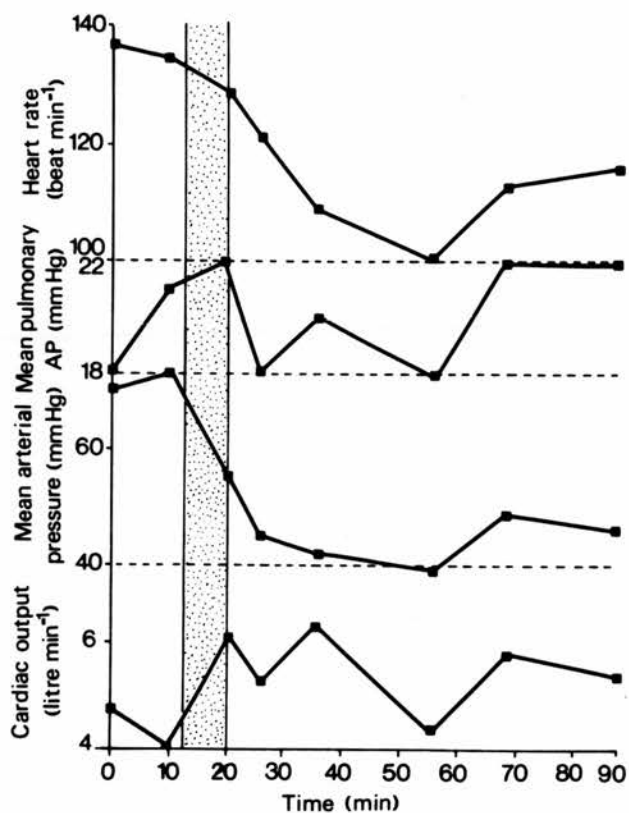
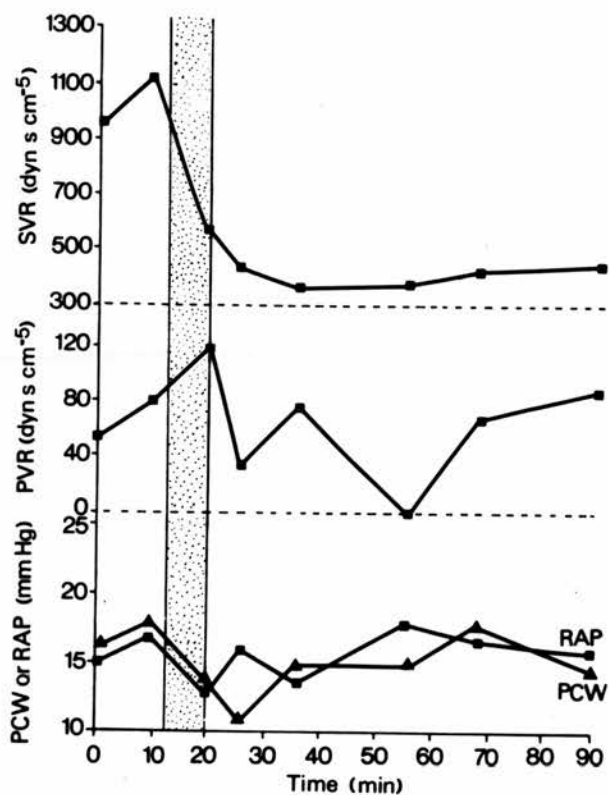


Figure 16.1: Changes in cardiovascular variables following release of increased intra-abdominal pressure (Patient 1). The dotted area represents the time during which decompression occurred. Methoxamine and ephedrine were administered at 55 minutes.

	Patient	Patient	Patient 3	
	1	2	a	b
Age (years)	35	25	33	
Sex	M	M	M	
Weight (Kg)	62	55	62	
<u>Transfusion Requirement between operations</u>				
FFP (mls)	1000	3500	1250	1000
Platelets	6	6	12	6
(units)				
Blood	13.6	22.4	14.7	16.2
(litres)				
HAS (mls)	1600	0	8000	1200
<u>Time between operations</u>				
(hours)	8	20	37	26
<u>Tamponade Volume</u> *				
(litres)	6	9	11	7

Table 16.1: Details of the three patients who underwent laparotomy for release of abdominal tamponade on four occasions. * Additional external blood loss through intra-abdominal drains.

Infusions of morphine and midazolam, administered for analgesia and sedation on the Intensive Care Unit, were continued up to the time of surgery at a dose of 3-5mg/hr for each agent. A period of stabilisation was allowed following induction of anaesthesia with fentanyl 50µg and ketamine 100mg; no neuromuscular blocking agents were administered. On account of the results of the intensive intraoperative monitoring of the first patient these two patients were monitored using the same techniques and rapid blood transfusion withheld. Peak airway pressures were noted and arterial blood was sampled at intervals for estimation of oxygen and carbon dioxide tensions and electrolyte concentrations. In one patient, end tidal CO₂ partial pressure (E_TCO₂) was monitored, together with both core and peripheral temperatures using temperature probes in the nasopharynx and on the foot. Haemodynamic measurements were made frequently throughout the perioperative period.

The haemodynamic measurements made before and after decompression of abdominal tamponade in patients 2 and 3 are shown in Table 16.2.

Parameter	Patient	Before Induction	After Induction	Before Decompression	After Decompression
HR (bpm)	2	122	121	120	107
	3a	125	120	120	110
	3b	125	113	111	109
MAP (mmHg)	2	69	80	76	35
	3a	70	60	69	67
	3b	56	57	59	38
MPAP (mmHg)	2	40	35	31	15
	3a	20	22	25	25
	3b	27	37	36	19
RAP (mmHg)	2	23	23	23	12
	3a	10	18	14	17
	3b	10	22	20	10
PCWP (mmHg)	2	30	30	32	18
	3a	13	14	19	17
	3b	13	22	22	10
CO (l/min)	2	5.0	4.3	3.6	4.9
	3a	7.5	6.4	7.4	10.2
	3b	11.4	11.7	10.3	12.2
SVR (dyn s cm ⁻⁵)	2	1008	1060	1177	376
	3a	644	525	594	392
	3b	322	239	302	183
PVR (dyn s cm ⁻⁵)	2			160	93
	3a	75	100	65	63
	3b	98	102	108	59
CT (deg C)	3b	37.3	37.1	37.0	36.7
PT (deg C)	3b	25.3	27.1	28.8	30.7
E _{TCO2} (kPa)	3b	5.5	5.7	5.6	7.2

Table 16.2: The haemodynamic changes seen before and after induction of anaesthesia and before and after decompression of abdominal tamponade in patients 2 and 3

Heart rate decreased on all occasions as did mean arterial pressure; there was an increase in cardiac output and a sharp decrease in systemic vascular resistance. Patient 3, during his first laparotomy (3a), was able to maintain cardiovascular stability better than on the subsequent occasion; mean arterial pressure was maintained by a considerable increase in cardiac output. During decompression, core temperature decreased slightly while foot temperature increased by 2°C. There were marked increases in hydrogen ion concentration, PaCO_2 and $\text{E}_\text{T}\text{CO}_2$ and a smaller increase in potassium concentration. There was no consistent change in PaO_2 or in ionised calcium or sodium concentrations.

The responses of the heart rate, mean arterial pressure, cardiac output and systemic vascular resistance of patients 2 and 3 to different sympathomimetic agents are shown in Table 16.3. Methoxamine had no effect on mean arterial pressure, cardiac output or systemic vascular resistance; however, ephedrine increased mean arterial pressure slightly by increasing cardiac output. Vasopressin increased mean arterial pressure to a greater extent and in a more appropriate way by increasing systemic vascular resistance but a greater rise in systemic vascular resistance was seen with bolus adrenaline administration. There was no evidence of an additive effect between the various agents administered.

	Patient	Before Methox- amine	After Methox- amine	Before Ephed- rine	After Ephed- rine	Before Vasop- ressin	After Vasop- ressin	Before Adren- aline	After Adren- aline
	2					10 u		b 0.3 mg i 4.0 mg/h	
	3a	10 mg		15 mg					
	3b	20 mg				7 u		b 0.3 mg	
HR (bpm)	2					10 u 107	120	b 120 i 127	127 137
	3a	109	111	109	133				
	3b	102	100			126 111	115 101	b 100 i 110	82 111
MAP (mmHg)	2					35	44	b 44 i 53	53 57
	3a	56	58	48	60				
	3b	44	51			65 45	87 67	b 51 i 48	107 74
MPAP (mmHg)	2					15	18	b 18 i 18	18 15
	3a	22	27	26	22				
	3b	16	17			32 20	36 25	b 17 i 20	27 24
RAP (mmHg)	2					12	18	b 18 i 10	10 9
	3a	15	19	15	12				
	3b	10	13			19 6	24 19	b 13 i 7	16 13
PCWP (mmHg)	2					18	20	b 20 18	18 15
	3a	17	16	16	11				
	3b	8	8			20 10	28 19	b 8 i 13	24 14
CO (l/min)	2					4.9	3.9	b 3.9 i 4.1	4.1 2.5
	3a	9.7	11.7	11.4	13.6				
	3b	10.3	9.9			12.9 10.6	11.3 9.7	b 9.9 i 10.9	10.0 12.9
SVR (dynes sec cm ⁻⁵)	2					376	533	b 533 i 839	839 1560
	3a	338	267	231	282				
	3b	264	307			285 294	446 395	b 307 i 300	728 378
PVR (dynes sec cm ⁻⁵)	2								
	3a	41	75	70	64				
	3b	62	72			74 75	56 49	b 72 i 51	24 62
CT (°C)	3b	35.8	35.8			35.7	35.7	b 35.8	35.8
PT (°C)	3b	28.8	28.3			30.6	30.2	b 28.3	27.7

Table 16.3: Cardiovascular changes observed in response to various sympathomimetic agents in patients 2 and 3.

b = bolus i = infusion page 531

Discussion

The immediate haemodynamic changes seen following release of raised intra-abdominal pressure have not been described previously. Richards and his colleagues (1983) reported the haemodynamic measurements from three patients before and after the release of abdominal tamponade - but over a longer time course and not during the operation. They observed decreases in mean arterial, central venous and pulmonary capillary wedge pressures after decompression but little alteration in cardiac output or systemic vascular resistance. Other studies on the effects of increased intra-abdominal pressure have been performed in patients undergoing laparoscopy (Kelman et al 1972; Lewis et al 1972; Motew et al 1973). These have produced less comprehensive results and conflicting measurements which appear to be dependent on the intra-abdominal pressure.

Studies in dogs have reported the changes seen with increasing intra-abdominal pressure (Richardson and Trinkle 1976; Toomasian 1978; Kashtan et al 1981); cardiac output decreased and systemic vascular resistance increased with increasing intra-abdominal pressure. This effect was most marked in dogs rendered hypovolaemic. The reduction in cardiac output was thought to reflect not only an increased systemic vascular resistance but also myocardial depression and a decrease in venous return. Alterations in pleural

pressure were insignificant and thought not to contribute to the haemodynamic changes.

The variability in cardiovascular indices observed in man may be the result of different degrees of arterial compression, of cardiovascular instability at the time, and of the concurrent treatment of this instability. The latter factors were minimized as far as possible while these patients were studied. Although intra-abdominal pressure was not measured, these patients appear to have had arterial compression as well as venous occlusion in the splanchnic and lower limb vessels. The increases in temperature at the foot, and in PaCO_2 , $\text{E}_\text{T}\text{CO}_2$ and hydrogen ion and potassium concentrations on decompression are evidence of re-established distal circulation following arterial compression. The increase in $\text{E}_\text{T}\text{CO}_2$ has been noted previously in similar patients (J V Farman, personal communication) and on several occasions since.

Before abdominal decompression, mean arterial pressure was maintained by blood transfusion; all patients had a tachycardia and right atrial and pulmonary capillary wedge pressures were increased. Patients 1 and 2 had a reduced cardiac output and normal systemic vascular resistance, but patient 3 had an increased cardiac output, with a low systemic vascular resistance. All three patients had a low pulmonary vascular resistance

but high mean pulmonary artery pressure.

Following abdominal decompression, there was an immediate increase in cardiac output, which was associated with a decrease in heart rate and an increase in stroke volume. There was a sharp decrease in systemic vascular resistance. Since the increase in cardiac output was smaller than the decrease in systemic vascular resistance, mean arterial pressure decreased, and since the main cause of the hypotension was a low systemic vascular resistance, vasoconstrictors were the most appropriate form of treatment.

Sympathomimetic agents were relatively ineffective in increasing systemic vascular resistance. Methoxamine had no effect and ephedrine, although it increased mean arterial pressure, did so by increasing cardiac output; systemic vascular resistance remaining low. Vasopressin is an endogenous vasoconstrictor with an important action on the splanchnic vascular bed. In these patients, it caused an increase in mean arterial pressure by increasing systemic vascular resistance. Adrenaline, which also causes splanchnic vasoconstriction, increased mean arterial pressure by increasing systemic vascular resistance when given by bolus administration. When given by infusion, adrenaline again increased systemic vascular resistance, and in Patient 2 this was sufficient to decrease cardiac

output so that mean arterial pressure did not increase. Vascular pooling may also occur as a result of vasodilatation of the splanchnic circulation and loss of tone of the intestinal smooth muscles - the latter occurring because of hypoxia resulting from the increased intra-abdominal pressure in these patients. The action of adrenaline is complex and may depend upon smooth muscle tone (Weiner 1985). Intensive monitoring is, therefore, advisable during its administration, particularly in this situation.

The haemodynamic changes described following abdominal decompression are compatible with the release of a high intra-abdominal pressure and the re-establishment of splanchnic and lower limb circulation. The splanchnic venous system is known to be an important blood reservoir (Greenway 1983) and maximal dilatation of these vessels would produce a system with a large capacity. Constriction of the splanchnic vasculature is mediated by alpha adrenoreceptors (Corday and Williams 1960; Hirsch and Rone 1982). These patients, however, responded poorly to sympathomimetic agents and required large doses of endogenous vasoconstrictors with a specific effect on the splanchnic circulation. This may be because of the presence of an abnormal circulation with maximally dilated vessels unresponsive to normal doses of sympathomimetic agents. This, in turn, may be a mechanical problem, with the vessels splinted open by

fibrous adhesions formed as a result of the patient's original pathology, or it may be that the alpha adrenoreceptors are poorly responsive, possibly on account of the release of vasoactive substances or toxins produced during tamponade. Chernow (1985) has postulated this type of mechanism based on a theory described by Berridge and Irvine (1984) and future pharmacological developments in alpha receptor modulators may elucidate its importance.

Although all these patients died eventually, none died with the ventilatory complications seen previously in similar patients, which may have been the result of overtransfusion. Since these patients, many others have been managed along the lines described above, with a large percentage now surviving to be discharged from the Intensive Care Unit; in particular, pulmonary complications resulting from fluid overload are uncommon. The frequent pulmonary complications previously seen in these patients may have been the result of inappropriate treatment of hypotension with excessive blood transfusion following abdominal decompression. Although some volume replacement is necessary during such operations, vasoconstrictors may be required in addition. Noradrenaline was not investigated in these patients because of the fear of adverse effects on renal function. Subsequently its use in this and other circumstances when a low systemic

vascular resistance has been encountered has shown this fear to be unfounded and its use associated with an improvement in renal function (vide infra).

Allowing the abdomen to tamponade, followed by laparotomy, will usually result in the bleeding stopping. Abdominal tamponade may be hastened by abdominal binding (van Obbergh et al 1989) or by use of pneumatic antishock garments (Aberg 1989). In a few patients, bleeding will continue despite these measures, and in such circumstances vasopressin might be expected to be useful. Vasopressin has long been known to reduce portal pressure (Clark 1928) and this has led to its use in the control of bleeding, particularly from oesophageal varices. Direct administration into the superior mesenteric artery was used to produce local haemostasis and to attempt to minimise systemic effects (Millette et al 1975; Melson et al 1976); however, intravenous administration has the same haemostatic efficacy and systemic effects (Barr, Lakin and Rosch 1975; Millette et al 1975; Johnson et al 1977) and is much simpler. Intermittent bolus administration of vasopressin reduces bleeding from oesophageal varices (Kehne, Hughes and Gompertz 1956; Shaldon and Sherlock 1960) but frequent short infusions (Conn and Dalessio 1962) or a continuous infusion (Barr, Lakin and Rosch 1975) may be more effective.

The ability of vasopressin to reduce pressure in the splanchnic vascular bed therefore prompted a trial of the intravenous use of vasopressin in an attempt to control intra-abdominal bleeding when conventional treatment proved ineffective. This study demonstrates the benefits of research in liver transplant patients to other groups of patients. Initially vasopressin was used in two patients, following liver transplantation, to control intra-abdominal haemorrhage when other therapeutic manoeuvres, including laparotomy, had failed. However, as experience with the drug grew it was used prior to laparotomy in other patients who had required surgery for other conditions. Ten patients are reported; six of whom were liver transplant patients and the remaining four had other causes for their intra-abdominal bleeding. Dr Maire P Shelly and Mr R Greateorex (Senior Registrar - General Surgery) assisted with the data collection.

***THE PHYSIOLOGICAL EFFECTS OF VASOPRESSIN WHEN USED TO
CONTROL INTRA-ABDOMINAL BLEEDING***

Intensive Care Medicine (1988) 14; 526-531

Patients

Ten patients suffering from major postoperative intra-abdominal bleeding received vasopressin over an eight year period and the case notes of these patients were reviewed retrospectively.

All the patients were exsanguinating from their intra-abdominal bleeding and all had impaired renal function from prerenal failure or acute tubular necrosis; four were requiring haemodialysis. Nine patients were receiving artificial ventilation. All were receiving infusions of fresh frozen plasma and platelet concentrates as well as calcium supplements; none had disseminated intravascular coagulopathy.

Vasopressin was diluted in 5% dextrose to form a solution containing 1 or 2 units/ml and administered using an accurate syringe driver. The dose administered was similar to that used for the treatment of oesophageal varices (Johnson et al 1977; Shaldon and Sherlock 1960) since the detailed pharmacokinetics of exogenous vasopressin in critically ill patients have not been evaluated.

Arterial and central venous pressures were measured directly via intra-arterial and central venous catheters; in addition, a continuous electrocardiogram, core temperature, urine output and nasogastric drainage were monitored in all patients. Additional parameters were measured as indicated. Hourly blood loss was calculated from measurements of external blood loss. The volume of blood and colloid required to maintain cardiovascular stability and any adverse effects of vasopressin were noted. The records of postmortem

examinations, performed on six of the patients, were reviewed. Student's paired t test was used to compare results where appropriate.

Results

The details of the patients and their surgical treatment before vasopressin was administered are shown in Table 16.4. Six patients had bled following liver transplantation, two after other forms of hepatic surgery and the remaining two had required surgery for intra-abdominal sepsis.

The duration of bleeding was 32.9 (17.3) hours [mean (SD)], with a measured nonoperative blood loss of 10.5 (4.9) litres and a blood transfusion requirement of 18.4 (11.2) litres prior to vasopressin treatment. In spite of the infusion of coagulation factors and platelets, the prothrombin ratio was 1.5 (0.3) and the platelet count was $84.7 (61.7) \times 10^9/l$.

Patient Number	Age (yrs)	Sex	Weight (kg)	Diagnosis	Bleeding Source	Surgical Management
1	14	F	59	chronic active hepatitis	gastric erosions	liver transplantation
2	57	M	67	α_1 -antitrypsin deficiency	peritoneum	liver transplantation, laparotomy
5	22	F	46	chronic rejection	liver and arteries near adrenal & oesophago-gastric junction	liver retransplantation
7	23	M	76	Budd Chiari	artery inferior to liver	liver transplantation
8	38	F	83	Wilson's disease	artery in retroduodenal lymph node	liver transplantation
10	28	F	55	hepatic failure	retroperitoneal area	liver retransplantation
<hr/>						
3	15	F	45	hepatoma	liver, into necrotic tumour	partial hepatectomy, laparotomy
4	60	M	78	hepatoma	liver surface	partial hepatectomy, laparotomy
6	39	M	65	intra-abdominal sepsis	peritoneum	drainage of abscesses
9	50	M	68	intra-abdominal sepsis	peritoneum and liver	drainage of abscesses, laparotomy

Table 16.4: Details of patients who received vasopressin and their surgical management before vasopressin treatment. Numbers refer to chronological order.

Bleeding

External blood loss was used as an index of bleeding and the change in the measured loss was used to assess response to vasopressin. Although occult losses are undetected, this provides an estimate of blood loss and follows the same trend as the change in transfusion requirement in individual patients. The estimated blood loss during the four hour period before giving vasopressin compared with the same period after its administration is shown in Table 16.5, together with vasopressin dosage for individual patients and the outcome of their bleeding.

In all but one of the patients blood loss decreased following vasopressin and the overall decrease in blood loss was significant ($p < 0.05$). In the liver transplant group, patient 1 had bleeding that was controlled by vasopressin alone. Of the remaining five patients, four required additional haemostatic laparotomy either before the vasopressin or afterwards to successfully control the haemorrhage (patients 2, 5, 7 and 10). Haemorrhage could not be controlled in patient 8. Patient 2 had an unsuccessful laparotomy to control haemorrhage before starting vasopressin and in patient 8 vasopressin was started before laparotomy to increase the time available for preparation.

Patient Number	4 h before vasopressin	4 hours after vasopressin	decrease in blood loss(%)	vasopressin treatment	Bleeding controlled
1	750	360	52	20 units bolus x 2	vasopressin alone
2	845	445	47	20 u/hr infusion 14 h	vasopressin following laparotomy
5	3500	3040	13	12-24 u/hr infusion 10 h	laparotomy following vasopressin
7	1593	966	40	10u/hr infusion 4 h	laparotomy following vasopressin
*8	325	170	48	20 units bolus x 1	not controlled
10	165	144	13	1-10 u/h infusion 132 h 5-10 u/hr infusion 12.5 h	laparotomy following vasopressin
<hr/>					
3	5459	5865	+7	10 units bolus x 2 20 units bolus x 1	not controlled
4	2495	1460	42	20 units bolus x 1 10 u/h infusion 12 h	vasopressin following laparotomy
6	600	500	17	2.5-10 u/hr 90 h	not controlled
9	945	730	23	2-7 u/hr infusion 124 h	vasopressin following laparotomy

Table 16.5: Blood loss during the 4 hour period before vasopressin administration compared with the 4 hour period immediately after, together with vasopressin dosage for individual patients and the outcome of their bleeding.

***Figures for 1 hr before and after vasopressin.**

In the four patients who had not received a liver transplant, laparotomy to control the haemorrhage had been performed in patients 3, 4 and 9 before starting vasopressin and although specific bleeding points were controlled, massive haemorrhage continued. Bleeding was controlled by vasopressin in two of these patients, but in patients 3 and 6 it was uncontrolled.

Mortality

Two patients (7 and 10) survived in the liver transplant group and were discharged from hospital. No patients in the other group survived. The three patients with bleeding uncontrolled by vasopressin or laparotomy died of their intra-abdominal bleeding within 24 hours of cessation of the vasopressin infusion. Patient 2 died of unrelated colonic bleeding (probably resulting from a rectal temperature probe) 18 days after control of his intra-abdominal bleeding by vasopressin. The other patients died of multisystem failure 15.2 (4.1) days after receiving vasopressin.

Cardiovascular Parameters

Changes in mean arterial pressure, heart rate and central venous pressure for periods before and after commencement and cessation of vasopressin infusion are shown in Figure 16.2 for both groups because of the small numbers in each group.

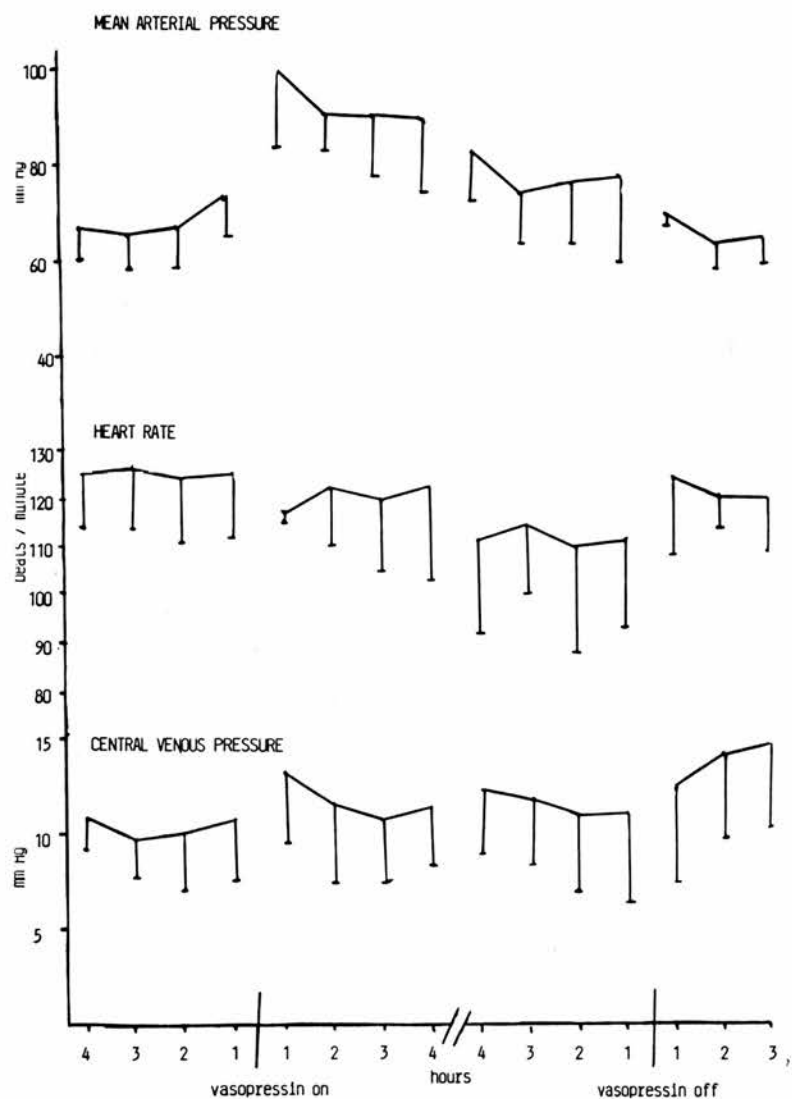


Figure 16.2: Mean (SD) arterial pressure, heart rate and central venous pressure for 3hr periods before and after commencement and cessation of a vasopressin infusion.

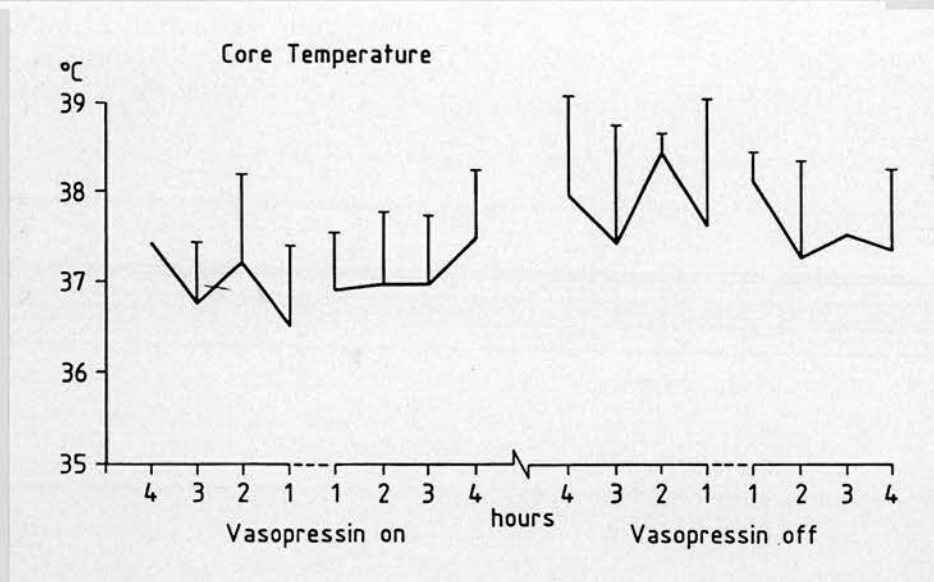


Figure 16.3: Core temperature (mean SD), for four hour periods before and after commencement and cessation of vasopressin infusion.

Mean arterial pressure increased with the start of the infusion ($p < 0.025$) but subsequently returned to baseline values when the infusion was stopped. A tachycardia was present in all patients before administration of vasopressin. Heart rate decreased during treatment but a tachycardia returned upon its cessation. The changes in central venous pressure were less marked but a transient increase coincided with the decreased heart rate on starting the infusion.

Urine output

The urine output of individual patients, for the 4 hour period before vasopressin treatment, compared with the 4 hour period immediately after, is shown in Table 15.6

Although the overall changes fail to reach statistical significance, they were of clinical significance. All patients initially had impaired renal function, but three of the liver transplant group (Patients 1, 2, 10) and two in the other group (3, 9) had a prompt diuresis when vasopressin was initiated.

Patient Number	4 hours before vasopressin	4 hours after vasopressin	% change
1	48	141	194
2	45	105	133
5	0	8	
7	38	34	-11
8*	26	22	-15
10	164	470	187

3	43	165	284
4	84	75	-11
6	214	250	17
9	50	101	102

Table 16.6: Urine output for individual patients for the four hour period before vasopressin compared with the four hour period immediately after. * Figures for one hour before and after vasopressin

Ischaemia

Myocardial. Dysrhythmias were documented electrocardiographically in two liver transplant patients (patient 2 had an episode of supraventricular tachycardia, patient 8 a period of bradycardia) and one other patient (patient 9 had a bradycardia together with ventricular ectopic beats) during vasopressin treatment. All these changes disappeared when the rate of infusion was reduced. Two patients in the liver transplant group (1 and 5) had diffuse myocardial myocytolysis noted at postmortem examination.

Intestinal. Two patients after liver transplantation had evidence of ischaemia. Patient 1 had pancreatic infarction and patient 2 colonic ulceration. The latter patient started to bleed profusely from his rectum postoperatively and it proved impossible to identify the site and control the bleeding. At postmortem a small circumscribed ulcer was identified at the presumed site of the rectal temperature probe. Colonic ulceration from rectal temperature measurement has not been reported previously and was not suspected in this patient. One patient (9) with intra-abdominal sepsis, after a vasopressin infusion lasting 125 hours, was found to have an infarcted appendix which was removed.

Hepatic. Four patients, all of whom were in the liver transplant group, had some evidence of hepatic

ischaemia. Patient 1 had areas of recent infarction 13 days after vasopressin administration, patient 2 had centrilobular necrosis, patient 8 had discrete areas of infarction and patient 5 had ischaemic necrosis.

Gastrointestinal motility

All the patients had an ileus immediately prior to treatment; nevertheless, evacuation of bowel motions occurred in three patients (patients 1, 9, 10) and the volume of nasogastric aspirate increased in patients 5 and 7. Patient 1 was in hepatic coma after liver transplantation and, in an attempt to improve her conscious level, she had a 4 litre enema before vasopressin treatment. The enema had been unproductive but vasopressin caused a prompt evacuation of her bowels and a slight improvement in her conscious level.

Other physiological effects

Temperature changes. The changes in core temperature, rectal or axillary, for the 4 hour periods before and after starting vasopressin and before and after its cessation are shown in Figure 16.3 for all ten patients. The increase in core temperature with the start of vasopressin infusion was statistically highly significant ($p < 0.0005$). In three patients, the core to peripheral temperature difference was monitored and remained unchanged.

Tachyphylaxis. Two of the patients, one in each group, who received prolonged vasopressin infusions appear to have shown tachyphylaxis. In patient 8 the infusion was continued at the same rate after bleeding was eventually controlled, in an attempt to allow haemostasis, but after 12 hours bleeding restarted with the infusion still in progress. Patient 9 required increasing doses of vasopressin to control his bleeding and when the infusion rate was reduced bleeding restarted.

Discussion

There have been a number of reports of the efficacy of vasopressin in the control of bleeding, particularly from oesophageal varices (Melson, Geisse and Stanley 1976; Shaldon and Sherlock 1960; Hussey 1985). These have stressed the haemostatic effect of vasopressin and mentioned various side effects. The group of patients reported here had massive intra-abdominal bleeding uncontrolled by conventional treatment. While the haemostatic effect of vasopressin was the primary objective of the treatment, the intensive monitoring of these patients during treatment allowed documentation of the physiological effects of vasopressin in critically ill patients during haemorrhage.

Vasopressin is a powerful vasoactive substance, known to decrease splanchnic blood flow (Eiseman et al 1960) and thought to act by constriction of splanchnic arteriolar

sphincters (Drapanas et al 1961; Nusbaum 1975). The haemostatic effect of vasopressin is, however, variable (Hussey 1985; Silva, Moffat and Walt 1969). This has been attributed to individual differences in hepatic blood flow characteristics and hepatic function (Hussey 1985; Nusbaum 1975) and vasopressin may be more effective in critically ill patients (Hussey 1985). The results from this group compare favourably with other reported series (Johnson et al 1977; Drapanas et al 1961). Vasopressin may, therefore, be used together with laparotomy in the management of patients with uncontrolled intra-abdominal bleeding following liver transplantation and major abdominal or hepatic surgery. A response to an initial bolus dose of vasopressin may indicate a more sustained response to its infusion. However, continued bleeding requiring a prolonged infusion of vasopressin indicates a poor response and increases the risk of complication. The high mortality rate seen in this group of patients reflects their severe illness and the influence of vasopressin cannot be determined accurately.

Patient 3 was the only patient who did not respond at all to vasopressin; she continued to bleed from the liver surface following an emergency partial hepatectomy for bleeding into a hepatoma. Patients 4 had similar bleeding following a partial hepatectomy for a hepatoma but he responded well to vasopressin. An important

difference between these patients was that patient 4 had a patent portal vein but the portal vein of patient 3 was occluded by tumour. The entire hepatic blood supply of patient 2 was, therefore, through her left hepatic artery (the right lobe of the liver having been surgically removed). While portal venous pressure decreases in response to vasopressin, the response of the hepatic artery is different, a biphasic response having been demonstrated in dogs (Bynum and Fara 1980). Initially, hepatic arterial flow decreases but this rapidly reverses so that 15-20 minutes after administration of vasopressin, hepatic artery flow increases to double the control value. The failure to achieve haemostasis in patient 3 may result from an increased hepatic arterial flow in response to vasopressin. Similar bleeding in patient 4 responded to vasopressin since he had a patent portal vein and total hepatic blood flow decreased.

The hypertensive effects of vasopressin have been previously reported in patients with oesophageal varices (Drapanas et al 1961; Edmunds and West 1962; Silva et al 1969; Nusbaum 1975). The increase in mean arterial pressure and central venous pressure and the decreased heart rate seen in these patients at the start of vasopressin administration may be due to the autotransfusion effect of splanchnic vasoconstriction, since the splanchnic vascular bed is a significant blood

reservoir (Hanson 1970).

When mentioned at all, previous studies have reported an antidiuretic effect of vasopressin (Edmunds and West 1962), and normally, release of vasopressin from the posterior pituitary causes an increase in renal tubular reabsorption of water. All the patients reported here had impaired renal function before treatment with vasopressin; the impressive diuresis experienced by five patients is, therefore, all the more significant and no patients became anuric. The mechanism for this increased urine output is unknown but may be related to an increased renal perfusion pressure with the increased mean arterial pressure. It is of note that noradrenaline, an agent also associated with the production of oliguria, has also been shown to increase urine flow in patients with septic shock (Meadows et al 1988; Desjars et al 1989; Hesselvik and Brodin 1989).

Myocardial ischaemia has been reported following vasopressin (Slotnik and Tieglund 1951) and it has been used as a stress test to provoke ischaemic changes (Ruskin 1947). Dysrhythmias related to vasopressin administration were seen in three patients. In addition, diffuse myocardial myocytolysis was found at postmortem examination in two other patients; this is a nonspecific change but vasopressin may have contributed to its development.

Intestinal ischaemia has been described following infusion of vasopressin into the superior mesenteric artery (Roberts and Maddison 1976; Beradi 1974; Renert et al 1972) but not following intravenous administration. The pancreatic and mucosal lesions are unlikely to have been due entirely to vasopressin, although it may have contributed to their development. The third patient had an infarcted appendix following prolonged vasopressin infusion and this would seem to be attributable to vasopressin.

Hepatic ischaemia has not been described before, and in this study, vasopressin cannot be conclusively incriminated since all the patients had livers that had been compromised by transplantation. It may, however, have contributed to the ischaemic changes seen.

Active peristalsis is a known feature of vasopressin administration and previous reports have described vomiting, diarrhoea and abdominal discomfort among its side effects (Collins and Root 1936; Shaldon and Sherlock 1960; Melson et al 1976). The increase in core temperature during vasopressin administration was a constant finding. In no patient did core temperature decrease. The corresponding increase in peripheral temperature suggests that this is not due to central diversion of blood flow with peripheral vasoconstriction but may be the result of increased heat production.

Vasopressin controlled intra-abdominal bleeding in two patients after liver transplantation and in two other patients. In a further two patients, vasopressin significantly reduced the rate of bleeding. The physiological effects of vasopressin varied between patients but there was a general improvement in haemodynamic parameters and six patients (three after liver transplantation and three after other surgery) had a diuresis following its administration. In some patients, vasopressin appears to be useful in the management of massive and uncontrolled intra-abdominal bleeding. However, because of the risk of ischaemic damage to other organs, vasopressin should only be used when conventional medical and surgical therapy has failed.

CHAPTER 17

THE CAUSES OF MORTALITY AFTER LIVER TRANSPLANTATION

IN THE INTENSIVE CARE PERIOD

Liver transplantation has been performed for 21 years in the joint programme between Cambridge and Kings College Hospital. In 1987 a retrospective analysis of the experience in the Cambridge/Kings College Series during the first 20 years of the programme attempted to identify the major causes of mortality of patients during their period in the Intensive Care Unit and provide information on the changing patterns of problems which have contributed to mortality. It was completed in the middle of 1988. I was assisted in this study with the data collection by Dr J Gomez-Arnau (Visiting Fellow).

MORTALITY DURING INTENSIVE CARE AFTER

ORTHOTOPIC LIVER TRANSPLANTATION

Anaesthesia (1989) 44: 959-963

Patients and Methods

During the period 1968 to the end of October 1987, 335 adult patients (over 14 years of age) have had at least one liver transplant in the Cambridge/Kings College Hospital Series. These patients were grouped according to a chronological scheme with the earliest group of 41 patients from 1968-1975, 60 patients from

1976-1980, 45 patients from 1981-1983 and 27-60 patients from each of the years 1984 to 1987. These groups were chosen as being of comparable size. The numbers in the groups from 1984 onwards represent a major increase in transplant activity in this hospital. Paediatric liver transplantation (now an increasing part of our practice) is not included in this study.

The place of death, time between operation and death, number of reoperations (if any), intraoperative blood transfusion, duration of stay in the ICU and the time of tracheal intubation were recorded on all patients who died. In the early part of the series, intensive care measures such as artificial ventilation, tracheal intubation, catecholamine infusion and invasive monitoring were practised outside the ICU but, for statistical purposes, these patients have been considered as if they had received this therapy and died in the ICU. The main cause of death was obtained from the postmortem results (when available) or from clinical data in the remaining patients, using criteria described previously (Cuervas-Mons et al 1986). When possible, only one (the major) cause of death was identified for each patient. Multisystem organ failure (MOF) was recorded as a cause of death when failure of two or more major organ systems was present. In this group of patients there are predominately three causes of multisystem organ failure; infection, infarction or

rejection of the donor liver. Infection was coded as the cause of death if there was microbiological confirmation of an organism (culture or serology). Infarction of the liver is characterised by a marked increase in the transaminases and prothrombin time and by sudden deterioration in the patients' condition. Rejection can be diagnosed histologically or by the response to pulsed bolus doses or steroids (Chapters 5 and 6). Infection, infarction or rejection was coded the primary cause of death if proven; multisystem organ failure was coded if no cause was identified. Renal failure was defined as the presence of a plasma creatinine level of $>217 \mu\text{mol/l}$, or if there was a need for haemodialysis or haemofiltration. All other concurrent pathology present at the time of death was coded as an associated diagnosis. Student's *t* test for unpaired data was used for statistical analysis where applicable.

Results

The numbers of patients who underwent orthotopic liver transplantation in each time period is shown in Table 17.1. One hundred and ninety five of the 335 patients who have received a liver transplant have died, 86 of them in the ICU (44%). Table 17.1 also shows the numbers of patients who died in the ICU during either their first admission or on readmission.

	1968-75	1976-80	1981-83	1984	1985	1986	1987
Number of patients	41	60	45	27	45	57	60
Age (years)(SD)	41.2(12.8)	40.4(12.2)	39.7(12.5)	37.4(13.5)	40.5(10.3)	41.4(10.8)	39.8(12.2)
Deaths in ICU							
(First admission)	9 (21%)	8 (13%)	12 (27%)	7 (26%)	6 (13%)	7 (12%)	5 (8%)
Deaths in ICU							
(Readmission)	4 (10%)	5 (8%)	8 (18%)	6 (22%)	4 (9%)	3 (5%)	2 (3%)
Deaths in ICU							
(Total)	13 (31%)	13 (21%)	20 (45%)	13 (48%)	10 (22%)	10 (17%)	7 (11%)

Table 17.1: Number (percentage of group) of deaths that occurred in the intensive care unit after orthotopic liver transplantation in the seven time periods.

The age and gender of adult patients who underwent liver transplantation did not change significantly during the study period, although the number of orthotopic liver transplants performed each year has increased steadily, particularly since 1984. The mortality rates for both the first and subsequent ICU admissions have decreased significantly since 1984. The main indications for transplantation are shown in Table 17.2. Initially a large number of patients were transplanted for malignancy but this has now become an uncommon indication. Alcoholic cirrhosis had the lowest ICU mortality and Wilson's disease the highest, although the small numbers prevent meaningful statistical analysis. The groups associated with the largest decreases in ICU mortality over the years are those with cryptogenic cirrhosis and malignancy.

The main causes of death are shown in Table 17.3. Infection has remained the most important cause of death (55%), with haemorrhage being the next most common (19%). Associated causes of death are shown in Table 17.4. Multisystem failure and renal failure make up 60% of all contributory causes of deaths. Multisystem (which would include renal) failure became increasingly recognised in the period 1981-1983 as the commonest cause of death.

	1968-75	1976-80	1981-83	1984	1985	1986	1987
	n d (%)	n d (%)	n d (%)	n d (%)	n d (%)	n d (%)	n d (%)
Biliary Cirrhosis	3 1 (33)	14 3 (21)	16 9 (56)	7 5 (71)	7 3 (43)	19 4 (21)	16 2 (12)
Chronic Active							
Hepatitis	2 0 (0)	7 1 (14)	7 3 (43)	5 3 (60)	9 2 (22)	8 1 (12)	13 1 (8)
Alcoholic Cirrhosis	1 0 (0)	3 0 (0)	1 0 (0)	1 0 (0)	1 0 (0)	1 0 (0)	5 1 (20)
Cryptogenic Cirrhosis	5 2 (40)	5 2 (40)	3 1 (33)	2 1 (50)	3 1 (33)	6 1 (16)	5 0 (0)
Sclerosing							
Cholangitis	- - -	2 0 (0)	2 2 (100)	- - -	4 1 (25)	4 0 (0)	4 1 (25)
Acute Liver Failure	- - -	- - -	- - -	3 1 (33)	1 0 (0)	5 2 (40)	6 0 (0)
Malignancy	29 10 (34)	21 4 (19)	11 3 (27)	6 1 (16)	13 1 (8)	5 0 (0)	5 1 (20)
Wilson's Disease	- - -	- - -	1 0 (0)	1 1 (100)	2 1 (50)	1 0 (0)	1 1 (100)
Budd Chiari	- - -	5 2 (40)	3 1 (33)	2 1 (50)	3 0 (0)	3 1 (33)	1 0 (0)
Other	1 0 (0)	3 1 (33)	1 0 (0)	- - -	2 1 (50)	5 1 (20)	1 0 (0)

Table 17.2: Primary diagnosis and mortality in the intensive care unit after orthotopic liver transplantation. n = number of patients. d = ICU deaths

	Deaths in the Intensive Care Unit							Deaths outside
	1968-75	1976-80	1981-83	1984	1985	1986	1987	ICU 1968-87*
Rejection	-	-	-	-	-	-	-	9 (9%)
Infarction	2 (15%)	1 (8%)	1 (5%)	1 (8%)	1 (10%)	-	-	6 (6%)
Infection	8 (62%)	7 (54%)	11 (55%)	8 (62%)	4 (40%)	4 (40%)	5 (71%)	30 (29%)
Haemorrhage	-	3 (23%)	3 (15%)	2 (15%)	3 (30%)	4 (40%)	1 (14%)	1 (1%)
Multisystem								
failure	1 (8%)	1 (8%)	4 (20%)	2 (15%)		1 (10%)	-	
Recurrence	1 (8%)	-	-	-	-	-	-	30 (29%)
Biliary								
anastomosis	-	-	-	-	-	-	-	3 (3%)
Pulmonary								
embolus	-	-	-	-	-	-	-	3 (3%)
GI Haemorrhage	-	-	1 (5%)	-	-	-	-	2 (2%)
Cerebral								
haemorrhage	1 (8%)	1 (8%)	-	-	1 (10%)	1 (10%)	1 (14%)	-
Other	-	-	-	-	1 (10%)	-	-	10 (11%)
Unknown	-	-	-	-	-	-	-	7 (7%)

Table 17.3: Main cause of death. Percentages refer to all deaths in that location in each time period.

*** excluding theatre deaths.**

	1968-75	1976-80	1981-83	1984	1985	1986	1987
Rejection	1 (8%)	-	-	-	-	-	-
Infarction	-	1 (8%)	-	-	1 (10%)	1 (10%)	-
Haemorrhage	-	-	1 (5%)	-	-	-	1 (14%)
Multisystem							
failure	1 (15%)	2 (15%)	14 (70%)	6 (46%)	3 (30%)	2 (20%)	2 (28%)
Biliary							
problems	1 (8%)	2 (15%)	1 (5%)	-	-	-	-
Pulmonary							
embolus	2 (15%)	1 (8%)	-	-	-	-	-
GI haemorrhage	-	-	-	-	1 (10%)	-	-
Renal failure	1 (8%)	-	9 (45%)	3 (23%)	1 (10%)	1 (10%)	1 (14%)
Cardiac							
failure	-	-	-	-	1 (10%)	1 (10%)	-
Disseminated							
intravascular							
coagulation	-	-	-	1 (8%)	-	-	-
Mesenteric							
thrombosis	-	-	-	-	1 (10%)	-	-
Miscellaneous	1 (8%)	-	-	1 (8%)	-	1 (10%)	-

Table 17.4: Associated causes of death in patients who died in ICU. Percentages are related to ICU deaths for that period.

During that period, renal failure occurred in 45% of patients who died in the ICU, much more frequently than previously. The relationship of renal failure to ICU mortality and one year survival can be seen from Figure 17.1. Many factors will influence survival, but the development of renal failure in critically ill patients is associated with high mortality. The decreasing incidence of renal failure in this group appears to be associated with a decrease in ICU mortality (except for 1987) and an increase in one year survival.

Table 17.5 presents further information on patients who died during admission to the ICU or after discharge. There is no statistically significant difference in age or gender. The average number of days spent in the ICU was shortest for those patients who survived but there was no statistically significant difference in duration of ICU stay between patients who died during their first ICU admission and those who died in their second ICU admission. Patients who died had a longer period of tracheal intubation in both admissions and required more intraoperative blood transfusion. The incidence of the main causes of death for all patients is shown in Figure 17.2.

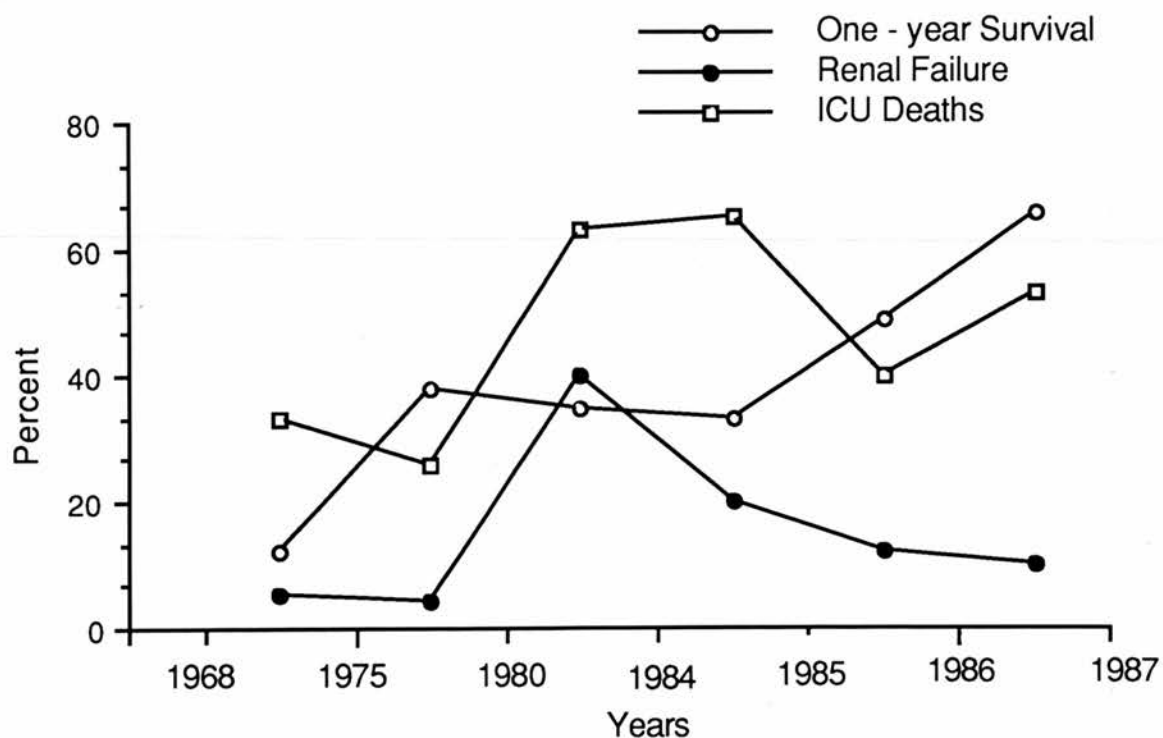


Figure 17.1: The incidence of renal failure during the period of intensive care in patients following liver transplantation from 1968 to 1987. Mortality (as a percentage of all deaths) and one year survival for the same period is also shown.

		Deaths during first admission	Deaths during readmission
	Deaths outside ICU (n = 81)*	to ICU (n = 49)	to ICU (n = 30)
Age	41 (12)	41 (10)	39 (12)
Sex	34 M 47 F	25 M 24 F	13 M 17 F
Survival time (days)	350.7 (600.6)	11.6 (10.6)#	89.1 (136.2)\$
ICU time (days)	6.1 (10.1)	11.6 (10.6)	10.9 (14.4)
Patient days	424	593	293
Intubation time (hours)	38.5 (78.9)	162.5 (200.4)@	124.2 (245.3)#
Intraoperative blood transfusion (litres)	8.1 (6.9)	19.6 (15.0)	9.8 (7.6)**
Total number of reoperations	43	34	16
Number of patients (%) of total) re-operated	35 (43%)	24 (49%)	12 (40%)
Re-operation/ patient ratio	1.2:1	1.5:1	1.3:1

Table 17.5: Risk factors associated with death after liver transplantation. Values are expressed as mean (SD). * excluding deaths in theatre. # p<0.01 (with respect to column 1). \$ p<0.01, ** p<0.05 (with respect to column 2).

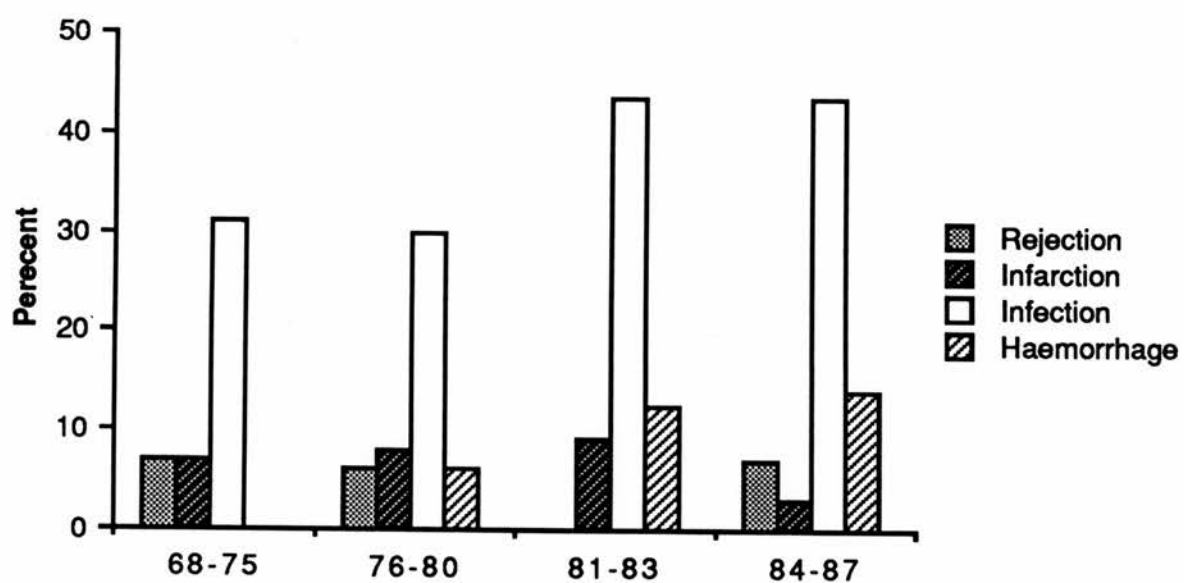


Figure 17.2: Main cause of death following liver transplantation for the period 1968 to 1987.

Discussion

The current one year survival after liver transplantation at this centre is 66%. This is higher than that reported by the European Transplant Registry (Bismuth et al 1987) and compares well with other series (Starzl 1986; Wall et al 1987; Memsic 1986). Survival has improved steadily from 12% during the first 8 years up to 49% in 1985 and 66% in 1986. The percentage of deaths in the ICU increased from 31% in the initial period to 48% in 1984 but since that time it has decreased each year to 11% in 1987.

Major changes in the management of these patients occurred in the study period. Postoperative artificial ventilation for the first 24 hours was introduced in 1976; prior to this period, patients were extubated at the end of operation and allowed to breath spontaneously (Farman et al 1976).

The period with the maximum incidence of multisystem organ failure including renal failure (1981-1984) coincides with the introduction of cyclosporin A, given immediately after liver transplantation, into clinical practice. This high incidence of renal failure caused a change in our therapeutic regimen. Cyclosporin is now administered 48 hours from the end of operation when the patient is haemodynamically stable and has adequate renal function. Further research

into renal protection led us to introduce low dose dopamine infusion as part of the routine management of these patients (Chapter 15). These changes and other more general measures (see below) were associated with reductions in the incidence of renal failure in patients who died, from 45% in the period 1981-1983 to 23% in 1984 and 10% in 1986. Simultaneously the one year survival rate increased to 49% and 66% in 1985 and 1986 respectively (Figure 17.1).

Infection continues to be the major cause of death in the ICU, an experience others have suffered (Cuervas-Mons et al 1986). Its total incidence appears not to have changed with time; it remains the primary cause of death in 35-45% of all patients and contributes to 55% of all ICU deaths. The high incidence of infection is a reflection of the severity of pre-existing illness, the magnitude of the operation and the need for immunosuppression. Selective decontamination of the digestive tract may help in reducing this problem, although its exact role in the critically ill remains to be defined (Johanson 1989; Sanderson 1989). New drugs for immunosuppression, such as FK506 (Starzl et al 1989), are currently under investigation in many parts of the world and their impact on the balance between prevention of rejection and the risk of infection remains to be determined. Almost all of the deaths caused by haemorrhage,

multisystem failure and cerebral problems occurred in the ICU. Multisystem organ failure is of considerable concern since there is so little that is treatable and the disease often exhibits a slow, remorseless progression until the patient dies. The Pittsburgh group (Miyata et al 1989) have demonstrated a correlation between the plasma concentration of endotoxin during the anhepatic period and the need for platelet transfusion, ventilatory support and mortality. Endotoxins are thought to mediate the majority of their effects principally through Tumour Necrosis Factor (TNF), a 17 kDalton protein produced principally by macrophages (Tracey et al 1986). If this theory is substantiated then the role of agents such as oxypentifylline, which prevents the formation of TNF by inhibiting the formation of the mRNA essential for its production (Zabel et al 1989), and monoclonal antibodies, which will inactivate TNF after its release (Celltech Ltd, Slough, Unpublished Information), may diminish mortality from this cause. An alternative approach to the prevention of MOF has been suggested by Fiddian-Green (1988). He believes that splanchnic ischaemia is a possible cause for MOF and following revascularisation of an ischaemic area free oxygen radicals are released, which produce organ damage. Free oxygen radicals are produced by xanthine oxidase, found principally in the mucosal epithelium, an enzyme which can be inhibited by drugs such as allopurinol (Grisham and Ganger 1989). If this theory is proved, then

pretreatment with allopurinol may also reduce mortality from MOF. Half of the deaths associated with ischaemic damage to the donor organ occurred in the ICU. No deaths attributed primarily to rejection, pulmonary embolism or biliary problems occurred in the ICU.

The volume of blood transfusion required intraoperatively appeared to be related closely to the ICU deaths occurring early in the postoperative period (Table 17.5). The mean blood usage in those patients who died in the ICU was 19.6 litres, more than reported by others (Butler et al 1985). This may reflect differences between patient groups or the routine use by other centres of veno-venous or veno-arterial bypass during the anhepatic period to reduce venous hypertension. Periods of hypotension, residual peritoneal blood clot and tamponade of renal vessels by large amounts of blood, resulting from bleeding, may lead to an increased risk of renal failure and infection. Patients who died in a subsequent ICU admission also had a larger blood loss than in survivors.

The duration of stay in the ICU and of tracheal intubation were, as might be expected, longer in the nonsurvivors (on average more than 10 days and 120 hours respectively).

Less quantifiable aspects of postoperative intensive

care concern the adoption of a management protocol in 1984, subsequently revised annually. Medical and nurse staffing levels have also improved during this time. Although no attempt has been made to analyse the effects of these developments others have shown that outcome in an ICU with adequate numbers of trained staff is better than in a unit with low staff numbers (Knaus et al 1986). During the review period, other factors, not directly related to the intensive care these patients received, will have also contributed to the improved survival. Improvements in donor maintenance and organ preservation (Chapter 2) and antibiotic prophylaxis have occurred and there has been a change in the diagnostic groups transplanted. Originally, a large number of patients were transplanted for malignancy. Unfortunately, many of these patients developed recurrence of their tumours and it is not now a common indication for transplantation. Patients with malignancy are usually transplanted more rapidly than others, with the result they tend to be less unwell than those with end-stage liver disease and so pose fewer perioperative problems, a feature demonstrated in their low overall mortality since 1975.

Eleven percent of patients died during the period of intensive care in 1987 despite improvements in management. Two major causes of mortality, infection and haemorrhage, require attention. It is of note that

these have remained essentially unchanged during this period. Some of the deaths diagnosed as infection may have been due to rejection and the fine balance between excessive immunosuppression, which may result in infection, and inadequate immunosuppression, with a consequent increased risk of rejection, requires careful management. Postoperative haemorrhage continues to be a problem and may represent surgical problems, derangement in the coagulation mechanism due to the pre-existing poor synthetic liver function and failure of synthetic function of the new liver.

APPENDIX I

ABBREVIATIONS AND NORMAL VALUES

Commonly used abbreviations

ABG	Arterial blood gas
A-aDO ₂	Alveolar arterial oxygen difference
ACT	α_1 -chymotrypsin
ADH	Antidiuretic hormone
AAG	α_1 -acid glycoprotein
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
APII	APACHE II score
AUC	Area under the time/concentration curve
CAVH	Continuous arterio-venous haemofiltration
CAVHD	Continuous arterio-venous haemofiltration with dialysis
CI	Cardiac index
Cl	Clearance
C _{max}	Maximum plasma concentration
CMV	Continuous mandatory ventilation
CO	Cardiac output
C _(t)	Plasma concentration at time t
CRP	C reactive protein
CT	Computerised tomography
CVP	Central venous pressure
CVVH	Continuous veno-venous haemofiltration
CVVHD	Continuous veno-venous haemofiltration

with dialysis

ECG	Electrocardiogram
EHBF	Estimated hepatic blood flow
$E_T\text{CO}_2$	End tidal carbon dioxide
FFP	Fresh frozen plasma
$F_I\text{O}_2$	Fractional inspired oxygen concentration
FRC	Functional residual capacity
GC-ECD	Gas chromatography with electrochemical detection
GC-MS	Gas chromatography with mass spectroscopy detection
GCS	Glasgow coma score
HABF	Hepatic arterial blood flow
HAS	Human albumin solution
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HR	Heart rate
ICB	Intercostal nerve block
ICU	Intensive care unit
IMV	Intermittent mandatory ventilation
IPPB	Intermittent positive pressure breathing
IV	Intravenous
IVC	Inferior vena cava
KPTT	Kaolin partial thromboplastin time
LFT	Liver function test
MAP	Mean systemic arterial pressure
MAC	Minimum alveolar concentration
MOF	Multisystem organ failure
MPAP	Mean pulmonary artery pressure

M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
n	Number
nc	Not calculated
NM	Normorphine
PA	Prealbumin
PBF	Portal blood flow
PCWP	Pulmonary capillary wedge pressure
PT	Prothrombin time
PEEP	Positive end expiratory pressure
PVR	Pulmonary vascular resistance
R	Respiratory quotient
RAP	Right atrial pressure
REM	Rapid eye movement
RIA	Radioimmunoassay
SaO ₂	Arterial oxygen saturation
SD	Standard deviation
SEM	Standard error of the mean
SIMV	Synchronised intermittent mandatory ventilation
SV	Spontaneous ventilation
SVR	Systemic vascular resistance
t _{½α}	Distribution half life
t _{½β}	Elimination half life
Tmax	Time to maximum concentration
V ₁	Volume of distribution of the central compartment
Vd	Volume of distribution
V _{ss}	Volume of distribution at steady state
V/Q	Ventilation perfusion ratio

Normal values

Plasma urea and electrolytes.

Sodium	132-142 mmol/l
Potassium	3.4-5.0 mmol/l
Glucose	3.5-9.0 mmol/l
Urea	≤7.5 mmol/l
Creatinine	35-125 μmol/l

Liver function tests

Bilirubin	2-17 μmol/l
Alkaline phosphatase	30-135 U/l
Alanine aminotransferase	7-40 U/l
Albumin	30-44 g/l
Total calcium	2.2-2.6 mmol/l
Ionised calcium	1.18-1.30 mmol/l

Arterial blood gases

Hydrogen ion	36-45 nmol/l
PaCO ₂	4.7-6.0 kPa
PaO ₂	9.3-14.0 kPa
Base excess	± 2.5 mmol/l
Standard bicarbonate	21-25 mmol/l

Urine

Creatinine clearance	90-120 mls/min
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Haematology

Haemoglobin	11.5-17.0 g/dl
Platelet count	150 - 300 $\times 10^9/l$
Prothrombin time (above control)	≤ 2 seconds
Kaolin partial thromboplastin time (above control)	≤ 7 seconds

APPENDIX 2

PUBLICATIONS ARISING FROM THIS THESIS Arranged in chronological order

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c = correspondence

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Correspondence

Small doses of frusemide increase urine flow in the critically ill

We observed that the administration of a single 20 mg dose of intravenous frusemide (the dose recommended in the manufacturer's data sheet and the British National Formulary¹) to critically-ill patients could produce a profound diuresis leading to hypovolaemia, dehydration and hypokalaemia. This particular group of patients are the least able to tolerate this embarrassment. These adverse effects have been noted previously in general medical patients.² We therefore recorded the diuretic response of critically-ill patients to low doses of frusemide.

Fifty-two critically-ill patients (30 male, 22 female, mean age 53.2 years [range 17 to 85]) received 5, 10 or 20 mg of frusemide intravenously, either to maintain fluid balance, or as part of the management of pulmonary and peripheral oedema. Eight patients received frusemide at more than one dose strength. Patients were excluded if they were hypovolaemic or if they had abnormal renal function. Pre-existing treatment was not changed in any patient; some may therefore have been receiving a renal dose of dopamine. When urine volumes in the four hours before and four hours after administration were compared they increased by 90%, 147% and 190% at the respective doses ($p < 0.05$). When the change in urine output was compared to the dose of frusemide, expressed as mg/kg body weight, the dose response relationship was highly significant ($p < 0.001$). The urine output increased by 133% for each 0.1 mg/kg of frusemide administered (one-way analysis of variance).

It has been reported previously that the oral administration of 20 mg frusemide produced a significant diuresis in water-loaded normal volunteers.³ This study demonstrated greater increases in urine output with smaller doses and may be a reflection of the increased and more rapid bioavailability of frusemide when given by the intravenous route.

We would suggest that the initial dose of intravenous frusemide in critically ill patients who do not have significant renal impairment should be 5 or 10 mg. Only if an unsatisfactory response is seen should larger doses be used.

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Table 1 Change in urine output after 5, 10 and 20 mg frusemide administered intravenously to 52 critically-ill patients

Dose of frusemide	5 mg	10 mg	20 mg
Mean % increase in urine output (SEM) (range)	90 (19.3) (-44 to 550)	147 (22.3) (-29 to 295)	190 (27.3) (96 to 310)
Number of patients	36	17	7

American literature review

Continued from page 186

measured at the same levels and in the livers of 13 treated and 13 control mice.

Bacterial translocation occurred in the endotoxin treated animals but not the controls. Xanthine oxidase and dehydrogenase activity were highest in the jejunums of both groups but were significantly reduced in the treated mice. However, in the ileum, caecum and liver, xanthine oxidase and dehydrogenase activity increased significantly. Histological injury in the endotoxin treated was limited to the ileum and caecum.

The finding that histological injury occurs in the same areas as increased xanthine oxidase and dehydrogenase activity does not establish a causal relationship between the two. However, the previous observation that inhibition of xanthine oxidase activity reduced mucosal injury suggests some relationship and that further studies may be fruitful.



SERUM ACUTE PHASE PROTEINS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

A. M. BURNS, M. P. SHELLY, S. WALKER AND G. R. PARK

SUMMARY

Acute phase proteins were measured in six patients before liver transplantation and for 72 h after orthotopic liver transplantation. The ability of the donor liver to mount an acute phase response was demonstrated, although the response was less than that seen in other groups of patients in whom this has been studied. Because of the reduced response to stress, the value of these measurements as indicators of liver function in this group of patients is limited.

KEY WORDS

Liver: transplantation. Liver function: acute phase protein synthesis.

Surgical trauma induces an acute phase reaction in which the liver is stimulated to switch from synthesis of albumin to production of a series of acute phase proteins [1]. These changes include normally a rapid increase in the synthesis of C-reactive protein and α_1 -antichymotrypsin, with a consequent increase in serum concentrations. Synthesis of α_1 -acid glycoprotein (AAG) is increased also, but to a smaller extent. Serum concentrations of pre-albumin decrease during an acute phase reaction more rapidly than those of albumin, and it may be regarded therefore as a "negative" acute phase reactant.

Immediately after orthotopic liver transplantation, the function of the donor liver is impaired because of the stress of two surgical procedures (donor and recipient) in addition to the cold and warm ischaemic damage sustained during the period between these operations. This study has investigated the ability of the recently transplanted donor liver to mount a stress response and synthesize acute phase proteins, and to assess their value as indicators of liver function immediately after liver transplantation.

METHODS AND RESULTS

The study was approved by the District Ethics Committee and informed consent was obtained before operation from seven consecutive patients. Patients received routine postoperative care in the intensive care unit and had an uncomplicated postoperative course, except for one patient who bled excessively and was excluded from further study.

Serum samples were collected immediately before orthotopic liver transplantation and after operation on arrival in the intensive care unit, then at 4-h intervals over a period of 24 h. Two further samples were collected at 48 h and 72 h. Subsequent analysis for C-reactive protein, α_1 -antichymotrypsin, AAG and pre-albumin was performed using specific immunoassay methods [2-5].

Changes in serum concentrations of the acute phase proteins in the 72 h after liver transplantation are shown in figure 1. There was a marked and sustained increase in serum concentrations of C-reactive protein and α_1 -antichymotrypsin after surgery. The increase in AAG concentration was not as rapid, with the maximal mean values being just above the upper limit of the normal range. Although serum concentrations of pre-albumin increased after operation, they remained well below the lower limit of the normal reference range.

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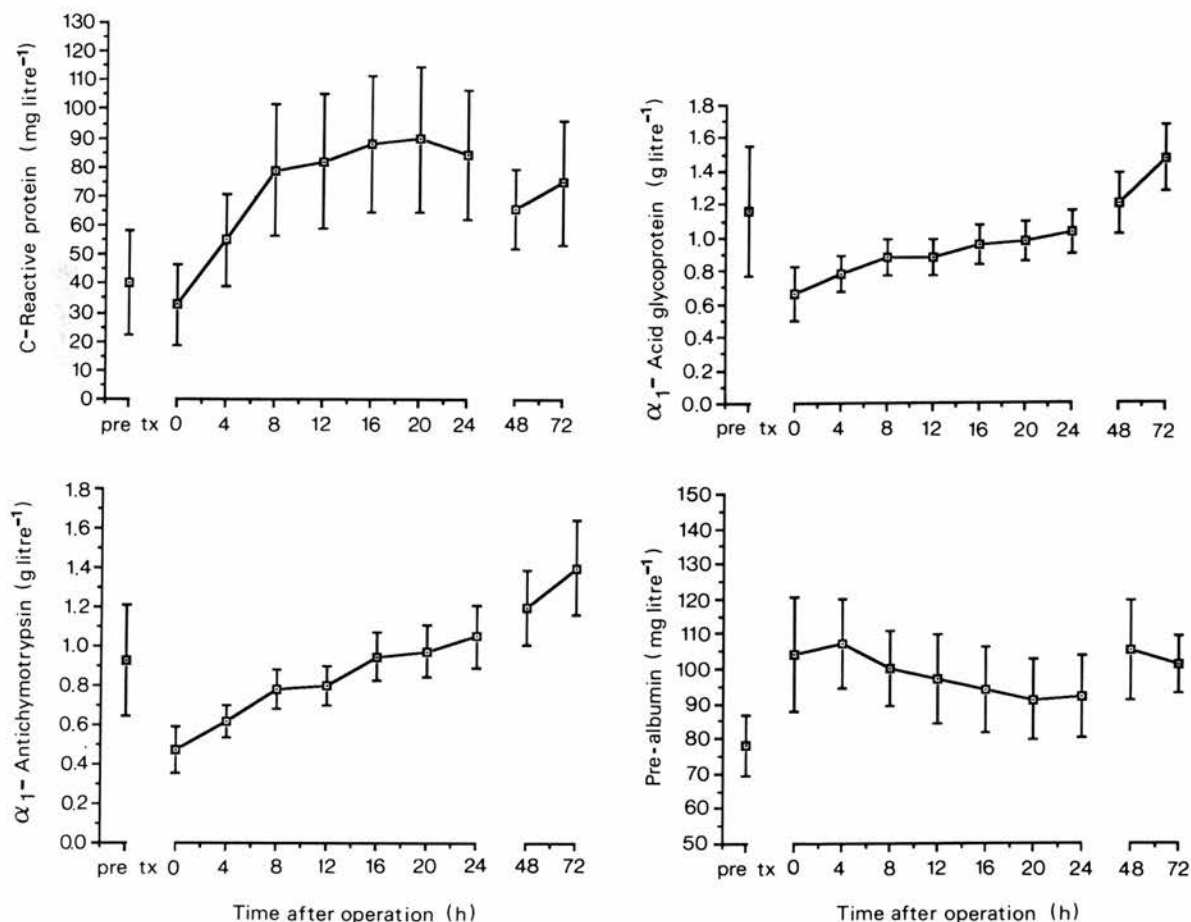


FIG. 1. Mean (SEM) concentrations of the acute phase proteins C-reactive protein (CRP), α_1 -antichymotrypsin (ACT), α_1 -acid glycoprotein (AAG) and pre-albumin (PA) before surgery (pre) and in the first 72 h after orthotopic liver transplantation (tx) in six patients. Normal ranges: CRP < 10 mg litre⁻¹; ACT 0.35–0.63 g litre⁻¹; AAG 0.5–1.0 g litre⁻¹; PA 150–355 mg litre⁻¹.

COMMENT

Monitoring of liver function after operation is important to detect adverse trends. This is particularly important after liver transplantation in patients who, in addition to the usual problems faced by the critically ill, may have episodes of rejection, infarction or infection. Conventional liver function tests are measured routinely, but alterations in enzyme and bilirubin concentrations may be relatively non-specific, and their interpretation following liver transplantation may be complicated by several factors [6].

Stress is a complex series of metabolic, endocrine and physiological processes. The acute

phase response includes the *de novo* synthesis and secretion of proteins by the liver; the rate of production might be used to assess liver function. The stimuli for the hepatocyte to synthesize these proteins, and the underlying cellular mechanisms, are not understood fully and the role of the stress response, particularly its prognostic significance, remains unclear. However, the stress response may reduce tissue injury and promote healing in association with enhanced host resistance [1].

In the immediate period after liver transplantation, when the stress response is still present, serum concentrations of acute phase proteins might be expected to provide an indicator of the synthetic function of the liver, improving liver

function being associated with increased serum concentrations of proteins and deterioration with decreased serum concentrations. This study demonstrated that the donor liver appears to be able to synthesize acute phase proteins, despite the ischaemic damage sustained before transplantation. However, the response was less than that reported previously in association with major tissue injury or bacterial infection. The moderate increases in acute phase proteins in our patients may reflect both dilution of the acute phase proteins by transfused blood and ischaemic damage to the donor liver resulting in a less than maximal response. Alterations in liver function may be associated with only minimal changes in protein concentrations and therefore their prognostic value as indicators of liver function is limited. Acute phase proteins may be used to complement conventional liver function tests as a guide to the function of the donor liver. However, further studies are necessary to define their exact role.

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Correspondence

Increases in oxygen consumption during administration of dopexamine in liver failure

We report a 22-year-old male with α -1 antitrypsin deficiency who developed fulminant hepatic coma precipitated by pneumococcal peritonitis. This was complicated by the subsequent development of a hyponatraemia of 109 mmol/L. Urgent liver transplantation was considered to be the treatment of choice and shortly thereafter a donor liver became available.

Since the patient was oliguric (urine output < 20 mls/hour) following volume resuscitation, it was decided to use a dopaminergic agonist to improve urine output.¹ Dopexamine Hydrochloride² was infused at 1 μ g/Kg/min and increased every 15 minutes to a maximum of 4 μ g/Kg/min. Haemodynamic variables and oxygen delivery and consumption were measured before starting the dopexamine and at the maximum dose (Table 1).

With increasing the dose of dopexamine there was little change in the haemodynamic parameters or oxygen delivery however, oxygen consumption increased markedly. Orthotopic liver transplantation occurred three hours after this study. Histological examination of the diseased liver revealed cirrhosis with infarction of

most of the right lobe as well as smaller infarcts in the left lobe.

The increase in oxygen consumption can be attributed to either a redistribution of blood flow to or within the splanchnic bed, or to an increase in metabolic rate induced by the administration of a sympathomimetic agent.

Dopamine has previously been shown to increase estimated hepatic blood flow (EHBF) under many conditions including peritonitis and haemorrhagic shock.^{3,4,5} The increased EHBF is usually associated with an increased cardiac output though the percentage increase in EHBF is greater than the percentage increase in cardiac output, implying some selective dilatation of the hepatic vasculature.⁶ Dopexamine, like dopamine, stimulates dopaminergic receptors of the DA₁ and DA₂ subtypes, though there is considerably less affinity for the DA₂ receptor than is seen with dopamine. Unlike dopamine, dopexamine has an action at the β_2 receptor. β -receptor stimulation has been shown to increase hepatic artery flow in dogs but the precise location of the receptors is unclear.⁷ The most likely cause for the increase in oxygen consumption seen in our patient is an improvement of distribution of blood flow to the

Table 1 Effect of increasing dose of dopexamine hydrochloride on haemodynamics and oxygen consumption and delivery in a patient with fulminant liver failure

Dose of dopexamine (μ g/Kg/min)	0	1	2	3	4
Heart Rate	120	115	115	123	120
Mean Systemic Arterial Pressure (mmHg)	60	69	63	62	61
Right Atrial Pressure (mmHg)	10	9	8	8	8
Mean Pulmonary Artery Pressure (mmHg)	15	15	14	14	14
Pulmonary Capillary Wedge Pressure (mmHg)	15	15	15	13	13
Cardiac Index (l/min/m ²)	4.98	5.24	5.01	5.19	4.99
Systemic Vascular Resistance (dynes/sec/cm ⁵)	408	470	449	423	433
PaO ₂ (KPa)	22.2				14.6
PvO ₂ (KPa)	7.8				7
SvO ₂ (%)	87.5				83.9
PaCO ₂ (KPa)	4.2				4.3
O ₂ Delivery (mls/min/m ²)	1176				1176
O ₂ Consumption (mls/min/m ²)	98				196

splanchnic bed, including the liver. Since cirrhotic livers have been shown to have portal vein - hepatic vein anastomoses, dopexamine may have exerted an additional effect in our patient by altering intrahepatic flow, including reperfusion of existing ischaemic areas.

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Complicated diabetic ketoacidosis

The management of severe diabetic ketoacidosis (DKA) is frequently complicated by gross systemic disturbances, accounting for the mortality of 5-15%.¹ We report a case of DKA which illustrates many of these complications.

A previously healthy 27-year-old woman presented in ketoacidotic coma. On admission she was noted to be obese, apyrexial, dehydrated, comatose (Glasgow Coma Scale 6), tachycardic (100 beats/min) but normotensive. She was profoundly acidotic (pH 6.79, PaCO₂ 1.45 kPa, PaO₂ 20.7 kPa, FIO₂ 0.21, base excess -39.2 mmol/l, arterial blood lactate 1.3 mmol/l) and ketonaemic. Biochemical analysis revealed a plasma glucose of 38.8 mmol/l, sodium 120 mmol/l, urea 15.8 mmol/l and amylase 1600 iu/l. The haemoglobin concentration was 17.9 g/dl and the white cell count 45.4 × 10⁹/l (predominantly neutrophils).

Conventional treatment with isotonic saline, intravenous actrapid and potassium chloride together with ampicillin, penicillin and metronidazole resulted in normoglycaemia within 10 hours but there was no improvement in her conscious level nor her acidosis. Blood samples screened for paracetamol and salicylate

were negative. The chest X-ray was clear and urine microscopy and culture showed no organisms. Abdominal and pelvic ultrasound revealed no obvious infection nor pancreatic abnormality and cerebrospinal fluid (CSF) was clear.

Her condition deteriorated and she was admitted to the intensive care unit (ICU) with cardiovascular instability (heart rate 120 beats/min, central venous pressure 21 cmH₂O, systolic arterial pressure 70 mmHg), respiratory embarrassment (rate 40/minute and widespread coarse crepitations) and renal failure (urine output 6 ml/hour, plasma urea 22.5 mmol/l, plasma creatinine 366 µmol/l, urine/plasma osmolality ratio 0.52 and plasma potassium 7.7 mmol/l). Despite inotrope support with dobutamine and adrenaline, she remained hypotensive. Initial haemodynamic measurements were pulmonary artery occlusion pressure 13 mmHg, cardiac index 4.9 l/min¹.m², oxygen delivery (DO₂) 747 ml/min¹.m², oxygen consumption (VO₂) 112 ml/min¹.m² and systemic vascular resistance index 538 dynes.sec/cm⁵.m². Nor-adrenaline was started and her cardiovascular status improved subsequently.

Over the next six hours, her diabetic control became difficult and infusions of up to 40 U/hour of actrapid insulin were needed; this appeared to be related to her catecholamine requirement. In the four hours following admission to the ICU, she received 500 mmol sodium bicarbonate; after this her pH remained above 7.0 without further treatment. Her plasma potassium returned to normal though her renal function continued to deteriorate in spite of dopamine and frusemide (250 mg).

By 48 hours her haemodynamic profile still suggested sepsis and aggressive efforts were made to find a source of infection. Examination of her ears, nose, throat, repeat abdominal and pelvic ultrasound scans, gynaecological assessment and abdominal laparoscopic examination revealed no abnormality. Repeated blood, sputum and urine cultures, viral studies and swabs from ears, nose, throat and vagina all failed to identify an infective source. At no stage was she pyrexial. She remained inotrope-dependent and at 60 hours continuous arteriovenous haemofiltration and parenteral feeding were started. Thereafter her condition gradually improved. Diabetic control with insulin consistently produced hypoglycaemia and six weeks after presentation her blood glucose was controlled by diet alone. She was generally well, neurologically intact and was discharged home.

This patient illustrated many of the biochemical abnormalities associated with severe DKA,² namely hyperglycaemia, deranged arterial blood gases, hyponatraemia, uraemia, hypophosphataemia, raised amylase, abnormal clotting and leucocytosis in the absence of infection. Despite standard treatment, multiple organ dysfunction supervened. She remained profoundly acidotic and comatose until NaHCO₃ was administered³ and it is reassuring that, in spite of prolonged severe acidemia, she made a full neurological recovery. The most likely reason for the patient's cardiovascular instability was septicaemia, with the underlying infection having precipitated DKA. Severe DKA may present a range of



PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER INTERCOSTAL NERVE BLOCK IN PATIENTS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

A. BODENHAM AND G. R. PARK

SUMMARY

Bilateral intercostal nerve blocks were performed on 12 occasions in 11 patients after liver transplantation. Group 1 (six patients) received bupivacaine 2 mg kg⁻¹ on one occasion; in group 2 (five patients) bupivacaine 2 mg kg⁻¹ with adrenaline 1:200 000 was injected on two occasions separated by 6 h. Arterial blood was sampled repeatedly and analysed for total bupivacaine concentrations by high performance liquid chromatography (HPLC). Six patients had bupivacaine concentrations within the putative toxic threshold of 2-4 µg ml⁻¹. The use of adrenaline-containing solutions neither slowed absorption reliably nor decreased peak concentrations of bupivacaine. Cumulation of bupivacaine occurred in group 2. No patient had adverse effects attributable to the bupivacaine.

KEY WORDS

Anaesthetics local: bupivacaine, plasma concentration. Anaesthetic techniques: intercostal.

Intercostal nerve blocks are an effective method of providing analgesia following both thoracic and abdominal incisions. This technique has been used successfully at this centre for several years to provide analgesia and reduce opioid requirements in patients after liver transplantation. There are, however, only limited data on the use of local anaesthetic agents in patients with liver disease. Patients with severe liver disease develop portal hypertension and extensive collateral vessel formation. The effects of these enlarged vessels on the rate of drug absorption is not known. In addition, the ability of the recently transplanted liver to metabolize drugs has not been established.

The long duration of action of bupivacaine makes it the drug of choice for intercostal nerve

block. We therefore measured total plasma concentrations of bupivacaine after intercostal blocks in patients who had undergone liver transplantation. Two groups were studied using bupivacaine with and without adrenaline, and after single and repeated injections.

PATIENTS AND METHODS

Eleven patients who required analgesia on the first or second day after liver transplantation were allocated consecutively to two groups:

Group 1 comprised six patients given a single set of bilateral intercostal nerve blocks using plain bupivacaine 2 mg kg⁻¹.

Group 2 consisted of six studies in five patients having two sets of bilateral intercostal nerve blocks separated by 6 h using bupivacaine with adrenaline 1:200 000 (2 mg kg⁻¹ for each set of injections). One patient was studied on two occasions, 4 months apart, after her first and second liver transplant.

Approval was obtained for the study from the hospital Ethics Committee and written informed consent was obtained before operation from each patient. The intercostal nerve blocks were performed when the patient was ready for tracheal extubation, usually on the first day after operation. A baseline blood sample was withdrawn from a radial arterial cannula, inserted previously for other purposes. Bilateral intercostal nerve blocks (T5-T10) were performed using a standard technique [1] by the same operator (A.B.). In

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smaller, wasted patients the dose of bupivacaine was made up to a minimum volume of 30 ml allowing an adequate volume of solution. Arterial blood (5 ml) was sampled at 5, 10, 15, 30, 60, 120, 240 and 480 min after injection of bupivacaine. In group 2 an extra sample was taken at 2.5 min and the final sample taken at 360 min, immediately before the intercostal blocks were repeated. Blood was collected in tubes containing lithium heparin as an anticoagulant and centrifuged at 3000 g. Plasma was stored at -20°C until required for analysis. Liver function tests (albumin, total protein and alpha-1-acid-glycoprotein (AGP)) were measured also in a baseline serum sample. Any adverse reactions such as changes in arterial pressure or neurological deterioration were recorded during this period. Detailed neurological assessment was not possible because of residual effects of opioids and benzodiazepines and the process of tracheal extubation. Care of the patient was, in all other respects including other drug therapy, as described previously [2].

Bupivacaine concentrations in groups 1 and 2 were compared by Student's *t* test for paired data. The relationship between bupivacaine concentrations and AGP concentrations was determined using linear regression analysis. Values are given as mean (SEM) except where indicated.

Analysis of samples

The assay was performed using HPLC as described by Nation, Peng and Chion [3]. After

the addition of an internal standard (etidocaine), the sample was alkalinized with sodium hydroxide and extracted with dichloromethane. An aliquot of extract was evaporated to dryness at 50°C and redissolved in a mobile phase of 1% triethylamine in water, adjusted to pH 3.0 with phosphoric acid and organic modifier (30% acetonitrile) before injection. The solution was injected onto a $150 \times 4.6\text{-mm}$ column containing $5\text{-}\mu\text{m}$ ultra-sphere "ods" and the flow rate was adjusted to 1.5 ml min^{-1} at ambient conditions. An ultraviolet detector at 205 nm was used. The assay was calibrated with spiked standards. All patients were receiving different medications, including morphine, midazolam, dopamine, prednisolone, azathioprine, cefotaxime, tobramycin, nystatin, ranitidine, folic acid and vitamin K. Control samples of serum from other liver transplant recipients who had not received bupivacaine revealed no interference with the assay. In addition to this study a further 2000 samples have been analysed and no interference from other substances detected [J. Goudie, personal communication]. The sensitivity of the assay was 50 ng ml^{-1} with a within-batch variation of 3.9% and a between-batch variation of 4.0%.

The AGP assay was performed by automated turbidimetric immunoassay using an IL Monarch analyser utilizing "Dako" antiserum to AGP.

Analysis of areas under the concentration-time curves were performed using an "Apple Fitter" programme. The values for $T_{1/2}^{\beta}$ and clearance in

TABLE I. Demographic data and presenting diagnosis of the patients in groups 1 and 2

Patient No.	Age (yr)	Sex	Weight (kg)	Presenting diagnosis
Group 1				
1	17	F	55	Chronic active hepatitis
2	56	F	45	Primary biliary cirrhosis
3	39	M	67	Sclerosing cholangitis
4	58	F	37	Primary biliary cirrhosis
5	29	F	60	Alcoholic cirrhosis
6	45	F	54	Primary biliary cirrhosis
Group 2				
7	26	F	55	Primary biliary cirrhosis (patient studied twice after two separate transplants)
8	52	M	80	Alcoholic cirrhosis + hepatoma
9	40	F	68	Chronic rejection of previous transplant for sclerosing cholangitis
10	59	F	64	Primary biliary cirrhosis + polycystic disease
11	21	F	43	Wilson's disease

TABLE II. Concentrations of plasma proteins and liver function tests in the 11 patients studied. ALT = Alanine transaminase; AGP = alpha-1-acid-glycoprotein; Alk. Phos. = alkaline phosphatase. * 1st transplant; ** 2nd transplant

Patient No.	Albumin (g litre ⁻¹)	Total protein (g litre ⁻¹)	AGP (g litre ⁻¹)	Bilirubin (μmol litre ⁻¹)	ALT (iu litre ⁻¹)	Alk. Phos. (iu litre ⁻¹)
Normal range	30-51	61-77	0.5-1.0	2-17	7-40	30-135
Group 1						
1	46	58	0.9	108	610	43
2	37	67	0.9	150	534	206
3	20	80	0.7	123	78	179
4	35	74	2.3	62	684	783
5	24	55	0.7	14	371	180
6	25	63	2.4	59	456	1200
Group 2						
7	27	51	1.4	867	115	978*
	31	45	1.6	249	674	963**
8	32	53	1.4	368	506	173
9	40	62	1.7	100	969	271
10	38	61	1.1	109	547	200
11	31	45	1.5	18	34	30

this study were not calculated, as sampling was not carried out for the recommended three elimination half-lives because of the need to repeat the injections for analgesia.

RESULTS

The details of the 11 patients studied are shown in table I. The injections were performed at a mean time of 15.7 (SD 8.5) h after the transplanted liver had been reperfused. The concentrations of plasma proteins and liver function tests at the time of each study are shown in table II.

The mean time to complete the bilateral intercostal nerve blocks was 4.5 (SEM 1.8) min.

In group 1 (plain bupivacaine) the mean maximum concentration (C_{max}) was 1.75 (SEM 0.07) $\mu\text{g ml}^{-1}$ (fig. 1). The time at which C_{max} was achieved (T_{max}) was 5, 10 and 15 min in three, two and one patients, respectively. The mean value of C_{max} , in group 2 (bupivacaine + adrenaline), was 1.69 (0.35) $\mu\text{g ml}^{-1}$ after the first injection (fig. 2). T_{max} occurred at 5, 10, 15 and 30 min in one, two, two and one patients, respectively. After the second set of injections in group 2, C_{max} was 1.99 (0.34) $\mu\text{g ml}^{-1}$. T_{max} occurred at 5, 10, 15 and 30 min in two, one, one and two patients, respectively.

C_{max} in group 1 was not significantly different from that after the first set of injections in group 2 ($P > 0.05$), indicating that the use of adrenaline

containing solutions did not reliably slow absorption. The plasma concentrations of bupivacaine had not returned to zero after 6 h in group 2, the time when the second set of injections were performed. In addition, the area under the mean concentration-time curve increased by 44% in group 2 after the second set of injections. These two factors indicate cumulation of bupivacaine. Eight patients had serum concentrations of AGP

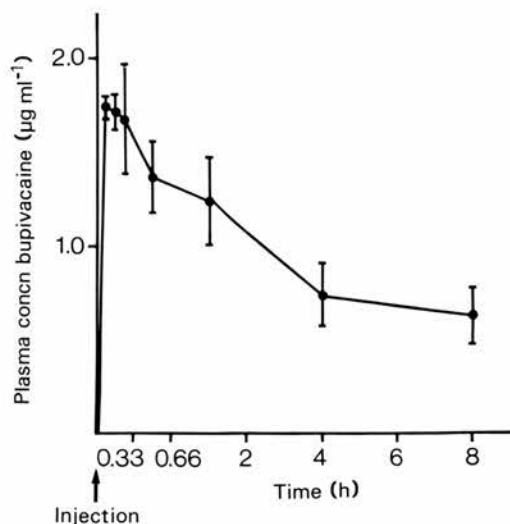


FIG. 1. Plasma concentrations of bupivacaine (mean, SEM) in group 1 after a single set of intercostal injections using bupivacaine 2 mg kg⁻¹.

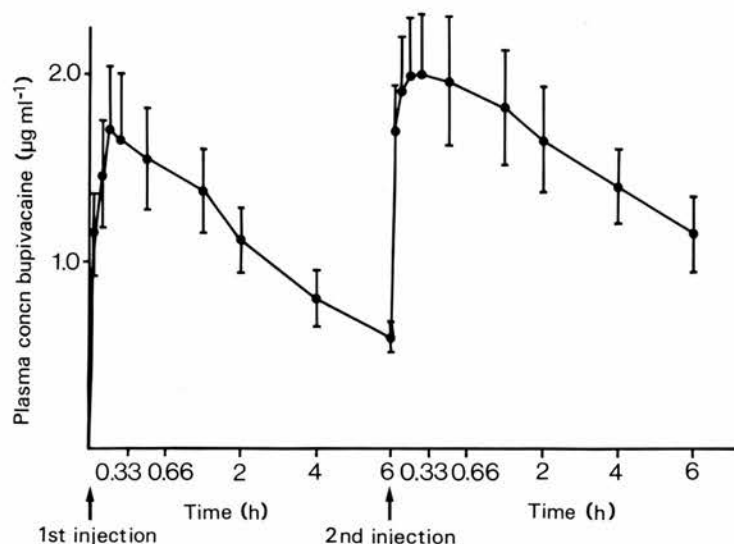


FIG. 2. Plasma concentrations of bupivacaine (mean, SEM) in group 2 after two sets of intercostal injections 6 h apart using bupivacaine 2 mg kg^{-1} containing adrenaline 1:200 000.

greater than the reference range (table II), but these increased concentrations did not correlate with the measured concentrations of total bupivacaine ($P > 0.05$). The patient who was studied twice had similar plasma concentrations of bupivacaine on each occasion.

DISCUSSION

Intercostal nerve blocks using bupivacaine are an effective method of providing analgesia following liver transplantation and are used routinely at this centre [2]. The technique is chosen in order to limit the dose of opioid. There has been one other short report of intercostal blocks after liver transplantation using bupivacaine in three patients [4]. This study used smaller total doses of 50–100 mg, making comparison of data difficult, but C_{max} occurred at times similar to our data at 5 min, the first sampling time.

Increased plasma concentrations of local anaesthetic may be a problem with intercostal blocks [5, 6] because of the large total volumes of drug solution required for multiple injections in a normally vascular area. In patients with advanced liver disease, the chest wall may have unusually large venous vessels because of porto-systemic anastomoses. These collateral vessels may alter the rate of drug absorption after intercostal injection.

The mean concentrations of bupivacaine were

within ranges similar to those reported in other series [5–7]. There was no statistical difference between C_{max} for the two groups with and without adrenaline. In group 1, the observation that C_{max} occurred at 5 min in two patients not given adrenaline suggests that C_{max} may have occurred earlier in some of these patients. In group II an additional sample was collected at 2.5 min, following reports of C_{max} occurring early [7]. No C_{max} values were seen at 2.5 min in group 2. T_{max} was variable between patients in both groups, but these cannot be compared reliably because of the spacing of sampling times and the relatively small numbers of patients studied. The addition of adrenaline to the bupivacaine solution did not consistently increase the time taken to reach C_{max} and this is in disagreement with other studies measuring arterial concentrations of bupivacaine after intercostal injection [7]. The abnormal vessels of patients with liver disease may not vasoconstrict normally in the presence of injected adrenaline. In addition, the size of the collateral vessels may not be important. Studies in children with extensive collateral vessel formation secondary to coarctation of the aorta have demonstrated that absorption of bupivacaine is the same as that of children with other forms of congenital heart disease without collateral vessel formation [6].

No adverse reactions were seen in these patients, despite plasma concentrations of bupi-

vacaine within the putative toxic range in six patients (two in group 1, four in group 2 following both sets of injections). This may reflect an inaccuracy of the reported toxic threshold of $2-4 \mu\text{g ml}^{-1}$ [8, 9] for bupivacaine. The reported toxic values have been derived from studies using short i.v. infusions of bupivacaine to obtain steady state concentrations. However, differences in the analytical method, sampling sites and infusion regimen used in these studies make interpretation difficult [10]. Alternatively, the lack of adverse side effects may be a reflection of residual benzodiazepine sedation, which had been administered before tracheal extubation [11]. All patients in the study were rousable but had residual sedation and analgesia, making neurological assessment difficult. In addition, the total bupivacaine concentrations measured in our study may not reflect the free, non-protein-bound concentration of the drug which is thought to cause CNS side effects [12].

Bupivacaine is bound extensively to AGP [13], an acute phase reactant with concentrations that were increased in these and other patients following liver transplantation, because of acute surgical stress and liver disease [Shelly, Walker, Burns and Park, unpublished observation]. In the presence of increased concentrations of AGP, increased total concentrations of bupivacaine would be measured, but toxicity might not occur, as the free concentration would be less. The concentrations of AGP were greater than the reference range ($0.5-1.0 \text{ g litre}^{-1}$) in seven of the patients in this study, but did not correspond to those with increased total bupivacaine concentrations. Unfortunately, it was not possible to measure free bupivacaine concentrations or the differing subtypes of AGP [14, 15] and their differing effects (if any) on drug binding. The relatively normal albumin and total protein concentrations reflect aggressive treatment of hypoalbuminaemia by infusion of albumin-containing solutions in the perioperative period.

Other factors also may have contributed to the increased plasma concentrations of bupivacaine. Uptake of bupivacaine by the lungs is significant [16] and may be inhibited competitively by drugs such as propranolol [17]. Three patients had been receiving propranolol for control of portal hypertension before liver transplant. However, these three patients did not develop consistently greater bupivacaine concentrations than the other patients studied. The presence of functional intra-

pulmonary shunting in patients with liver disease [18] may also increase the availability of the drug to the systemic circulation. This has been shown experimentally in animals, using lignocaine [19].

Bupivacaine is metabolized by the liver, with a lesser hepatic extraction ratio than lignocaine [10, 20]. Little is known of drug metabolism shortly after liver transplantation, but studies to date have shown both normal and abnormal pharmacokinetics for several drugs. The transplanted liver is subject to insults during two operations (removal from the donor and insertion into the recipient), with a varying ischaemic time between. Clinical studies have shown that clearance of lignocaine may be impaired in patients with cirrhosis [21], after hepatectomy [22], and during viral hepatitis [23]. No data exist for bupivacaine.

Extrapolation of these results to other patients with liver disease requires caution, as differences in the mechanisms of liver injury may alter its capacity to eliminate bupivacaine. However, the results suggest that caution may be necessary in this group of patients when intercostal blocks are performed. Some patients may achieve potentially toxic plasma concentrations of bupivacaine at a variable time after performing the intercostal nerve blocks. The use of adrenaline-containing solutions did not consistently reduce the speed of absorption or the maximum concentration of bupivacaine. Furthermore, bupivacaine cumulation after repeated intercostal nerve blocks within 6-8 h may occur in some patients following liver transplantation, and possibly others with hepatic dysfunction.

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M.D., 1991



CHANGES IN ALVEOLAR-ARTERIAL OXYGEN PARTIAL PRESSURE DIFFERENCE DURING ORTHOTOPIC LIVER TRANSPLANTATION

K. R. BURCHETT, M. F. SMITH AND G. R. PARK

SUMMARY

Changes in the alveolar-arterial oxygen partial pressure difference ($PA_{O_2} - Pa_{O_2}$) were measured in 39 patients undergoing orthotopic liver transplantation without veno-arterial or veno-venous bypass. The operation can be divided into an initial dissection phase, an anhepatic phase when the hepatic artery, portal vein and vena cava are clamped, and a post-anhepatic phase after the vascular clamps are released. There was an initial increase in ($PA_{O_2} - Pa_{O_2}$) during the dissection phase, followed by an immediate decrease when the liver was removed. This decrease continued throughout the anhepatic period, but a further increase in ($PA_{O_2} - Pa_{O_2}$) occurred after release of all the vascular clamps and during abdominal closure.

KEY WORDS

Oxygen: ($PA_{O_2} - Pa_{O_2}$). Surgery: liver transplantation.

The observation during an orthotopic liver transplant operation that the arterial oxygen tension (Pa_{O_2}) remained low despite increasing the inspired oxygen concentration (FI_{O_2}) until removal of the liver, when a marked increase in Pa_{O_2} was noticed, prompted us to review the anaesthetic records of the previous 20 liver transplant operations. This suggested an improvement in arterial oxygenation during the anhepatic phase. We therefore studied prospectively 40 consecutive patients undergoing liver transplantation and measured the alveolar-arterial oxygen partial pressure differences ($PA_{O_2} - Pa_{O_2}$) at various stages during the procedure.

PATIENTS AND METHODS

We studied 40 consecutive patients undergoing orthotopic liver transplantation. The anaesthetic

technique used was at the discretion of the anaesthetist, and consisted of artificial ventilation using either air-oxygen and isoflurane or nitrous oxide-oxygen with isoflurane, fentanyl, or both. Neuromuscular block was maintained by an infusion of either atracurium or vecuronium.

As part of the routine monitoring of these patients, arterial blood samples were taken and analysed immediately for oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions (Corning 178 pH/blood-gas analyser) at the following stages during the procedure: (A) after induction of anaesthesia, and before the start of surgery; (B) during dissection of the liver; (C) at the beginning of the anhepatic phase; (D) at the end of the anhepatic phase (after unclamping of the suprahepatic vena cava and the hepatic portal vein); (E) after full restoration of inferior vena cava flow and (F) during abdominal closure. The inspired oxygen concentration (FI_{O_2}) was measured continuously throughout the operation (Engstrom Eliza Duo O_2/CO_2 analyser). The values for Pa_{O_2} and Pa_{CO_2} were corrected for the patient's core temperature at the time of sampling using a standard nomogram [1], and the alveolar oxygen tension was estimated using the formula $PA_{O_2} = PI_{O_2} - (PA_{CO_2}/R) + (PA_{CO_2} \cdot FI_{O_2} \cdot (1 - R)/R)$. The respiratory quotient, R , was assumed to be 0.8, and it was assumed that $PA_{CO_2} = Pa_{CO_2}$.

Changes in blood volume and composition were minimized by utilizing invasive haemodynamic monitoring and measurements of packed cell volume at each time point.

Data were analysed using Student's paired t test adjusting for the Bonferroni inequality [2].

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TABLE I. Mean (SEM) FI_{O_2} , Pa_{CO_2} , Pa_{O_2} . A = After induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation

	A	B	C	D	E	F
FI_{O_2}	0.42 (0.02)	0.42 (0.01)	0.43 (0.02)	0.44 (0.01)	0.43 (0.01)	0.44 (0.01)
Pa_{CO_2} (kPa)	3.9 (0.13)	4.0 (0.14)	3.8 (0.11)	4.8 (0.11)	4.5 (0.12)	4.4 (0.12)
Pa_{O_2} (kPa)	21.4 (1.61)	18.5 (1.64)	22.5 (1.53)	24.2 (1.21)	23.0 (1.2)	20.1 (1.56)

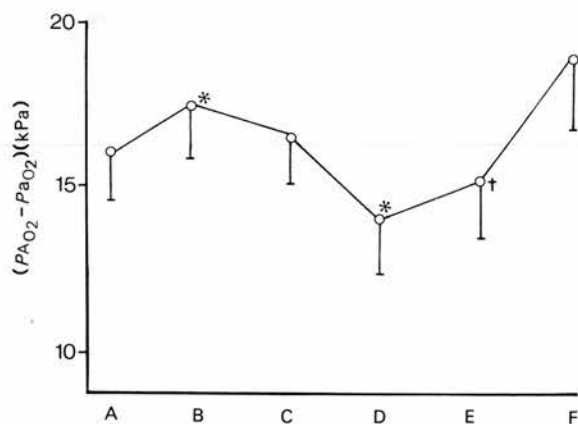


FIG. 1. Mean (SEM) changes in $(PA_{O_2} - Pa_{O_2})$ liver transplantation in 39 patients. A = After induction; B = during liver dissection; C = start of anhepatic phase; D = end of anhepatic phase; E = inferior vena cava anastomosis; F = abdominal closure. Statistically significant differences ($P < 0.01$): *B-D and D-F; †E-F.

Four comparisons were made (A with B, B with D, D with F and E with F). All data are presented as mean (SEM).

RESULTS

Complete records were available for 26 female and 13 male patients, with a mean age of 33 yr (range 1-63 yr). There was an initial decrease in Pa_{O_2} and an increase in $(PA_{O_2} - Pa_{O_2})$ during dissection of the patient's liver (A to B) from 16.0 (1.5) to 19.1

(1.6) kPa (table I, fig. 1). The increase in $(PA_{O_2} - Pa_{O_2})$ failed to reach statistical significance. During the anhepatic phase there was a decrease in $(PA_{O_2} - Pa_{O_2})$ which continued to a nadir at D (14.3 (1.6) kPa). After revascularization of the donor liver, the alveolar-arterial gradient again increased, and this continued through E (15.1 (1.5) kPa) to abdominal closure at F (19.1 (1.8) kPa). The differences between B and D, E and F, and D and F were significant ($P < 0.01$). No correlation was found between the changes in $(PA_{O_2} - Pa_{O_2})$ and the anaesthetic technique used.

Packed cell volume and the amount of fluid transfused at each stage are shown in table II. Despite the large volumes transfused, there was little change in arterial pressure. The haematocrit increased during the anhepatic period, because of the infusion of blood with a high haematocrit from the cell saver system used for autotransfusion [3].

DISCUSSION

An increase in $(PA_{O_2} - Pa_{O_2})$ during routine, uncomplicated anaesthesia is well recognized, and is attributed to a 20% decrease in functional residual capacity (FRC) and an increase in ventilation/perfusion (\dot{V}/\dot{Q}) mismatch. The reduction in FRC with general anaesthesia occurs during artificial and spontaneous ventilation, but increasing the FRC following induction of anaesthesia does not reverse abnormal gas exchange. Atelectasis occurs in the dependent parts of the

TABLE II. Mean (SEM) packed cell volume (PCV), systolic arterial pressure (SAP) and volume of fluid transfused (Fluid). A = After the induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation

	A	B	C	D	E	F
PCV (%)	30.9 (1.1)	32.1 (1.1)	36.6 (0.9)	39 (1.0)	33.8 (1.2)	34.5 (1.1)
SAP (mm Hg)	111 (3.2)	116 (3.1)	105 (3.0)	106 (4.5)	111 (4.6)	111 (3.3)
Fluid (ml)	226 (87)	1420 (219)	3345 (456)	5339 (649)	6278 (739)	10833 (2478)

lung, the low compliance of this part and the immobility of the adjacent portion of the diaphragm preventing full expansion of the dependent lung [4]. ($PA_{O_2} - Pa_{O_2}$) is increased also by a reduction in cardiac output, an increase in PA_{O_2} or a reduction in haemoglobin concentration [5]. The increase in ($PA_{O_2} - Pa_{O_2}$) during the dissection phase and towards the end of the procedure during abdominal closure may be explained by an initial reduction in FRC because of cranial displacement of the diaphragm, leading to atelectasis in the dependent parts of the lungs and consequent increase in \dot{V}/\dot{Q} mismatch. When the liver has been removed (during the anhepatic phase) this process may be reversed because the reduction in abdominal contents and surgical retraction allow freer movement of the diaphragm. These mechanisms result in an increase in FRC, or a decrease in atelectasis, or both, in the dependent part of the lung, which may account for the gradual improvement in the ($PA_{O_2} - Pa_{O_2}$). These factors would be reversed when the donor liver was in place, and may explain the subsequent increase in ($PA_{O_2} - Pa_{O_2}$). The reduction in cardiac output at the beginning of the anhepatic phase as the vena cava is cross clamped [6] may be expected to increase ($PA_{O_2} - Pa_{O_2}$), but the reduction in oxygen consumption of some 25% seen on removal of the patient's liver [7] may balance this to some extent. If the reduction in oxygen consumption results in an increase in the mixed venous oxygen content, and if there is a significant pulmonary shunt, there should be an increase in arterial oxygenation, as the oxygen tension in the shunted blood would have increased and have a

smaller effect in reducing Pa_{O_2} . However, it is more likely that the reduction in cardiac output results in a decrease in mixed venous oxygen saturation, albeit less than expected because of the decrease in oxygen consumption. The most likely explanation for the observed improvement in ($PA_{O_2} - Pa_{O_2}$) is thus an improvement in the \dot{V}/\dot{Q} ratio secondary to an increased movement of the diaphragm. An alternative, but unlikely, explanation is that the liver is secreting a vasoactive substance which is affecting the pulmonary vasculature.

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quire lengthy ventilator management and those patients acutely ventilated for respiratory failure where high peak airway pressures may be a concern, or who consistently oppose volume-limited approaches to ventilation. As with any new therapeutic modality, discussion seems to generate more questions than answers. The introduction of IPS raises many issues concerning approaches to weaning and methods of optimizing ventilatory muscle function, as well as providing ventilatory support in general. The data provided by Tokioka et al. will clarify some of the questions about its physiologic effects and application. Its use should be encouraged but should be based on available scientific data.

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Review articles

Care of the multiple organ donor

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Abstract. Successful organ transplantation offers patients with end stage organ failure the chance of a normal life. The recognition of brain death allowed the use of beating heart donors and this has enabled multiple organ procurement from a single donor. Suitable patients with severe brain injury resulting in brain death, who may be potential organ donors, are to be found on both neurosurgical and general intensive care units. The pathophysiological results of brain death are similar, irrespective of the underlying cause. Severe brain injury may result in the loss of temperature regulation, and the development of diabetes insipidus and cardiovascular instability. The management of brain injury before death often results in abnormalities of fluid balance, due to fluid restriction and diuretic therapy. Other problems such as acute endocrine failure and the impact of their correction on ultimate organ function remains to be elucidated. Good donor maintenance in the intensive care unit and operating theatre is essential if optimal function of the transplanted organ is to occur.

Key words: Organ donor – Critical care

The first successful transplantation of organs in humans took place in 1954 with the transfer of a kidney from one identical twin to another [1]. This followed the first reported human renal transplant by Voronoy in 1936 and later attempts in the early 1950s. Shortly thereafter kidneys were successfully transplanted from non-identical siblings using ionising radiation to provide immunosuppression. Since these early beginnings many different organs have been successfully transplanted. The kidney is able to withstand periods of ischaemia at body temperature for up to one hour

(warm ischaemic time) and still function satisfactorily after transplantation. This allows the removal of kidneys after the circulation has ceased. The heart, liver and lungs will tolerate only short periods of warm ischaemia before irreversible cellular damage occurs. These organs must be isolated whilst the donor circulation is intact and cooled with cold perfusion fluids whilst in situ. The concept of brain stem death was coincidentally becoming accepted at the same time as these needs were recognised and this has allowed the use of beating heart organ donors.

Brain death was first described by Mollaret and Goulon in France during 1959 [2] and was formally accepted in the United Kingdom (UK) during 1976 [3]. The initial aim was to prevent the unnecessary prolongation of therapy when a hopeless prognosis exists. Since then large studies have repeatedly shown the validity of the diagnosis of brain death [4].

The success of transplantation has increased the demand for organs which has resulted in the removal of multiple organs from one donor. Studies after multiple organ procurement have shown no individual difference in organ function when compared with single organ donation [5]. It has been estimated that there are approximately 4000 potential donors per year in the UK but only 15–20% of these actually donate organs [6, 7]. These figures are derived from epidemiological studies of the incidence of subarachnoid haemorrhage and severe head injuries. They do not take into account regional variations in medical practice or pathology. In addition changes in patient admissions relating to seat belt and drunk driving legislation may have reduced the incidence of major head injury. Assertions, based upon these figures, that many potential organ donors are missed each year [8] may not be true. Studies in this centre have demonstrated that few suitable donors are lost (unpublished observations). The exact numbers of potential organ donors in the UK is

still unknown and it is hoped that a national study in 1989 will provide this information.

It is vital, for optimal organ function after transplantation, that the donor organs are kept in good condition [9] with particular emphasis placed on the maintenance of organ perfusion. Furthermore, if during life, the patient wanted to donate organs then the medical team have an obligation to ensure that organs are in the best possible state for the recipient.

The diagnosis of brain death

In the UK the donor must have satisfied the brain stem death criteria as defined by the Medical Royal Colleges in 1976 [3]. Other countries in the western world have set similar criteria. In the UK these criteria are based on clinical findings [10–12] and do not include electroencephalograph (EEG) examination and cerebral blood flow measurements that are mandatory elsewhere [13, 14]. The causes of death in beating heart donors during one year (1987), as reported to the United Kingdom Transplant Service, are shown in Table 1.

Tests for the criteria in the UK must be performed by 2 consultants or a consultant and senior registrar, who must be clinically independent and unconnected with the transplant team. The diagnosis must be certain, the patient having suffered severe and irreversible brain damage, the aetiology of which must be known and be totally dependent upon artificial ventilation. If any doubt exists then the diagnosis of brain death must not be made. Hypothermia, metabolic and endocrine abnormalities should be excluded. Prolonged drug action including alcohol should always be considered and can only be excluded by the passage of time. Measurement of plasma concentrations of sedative and analgesic drugs has been shown to correlate poorly with central effects [15] and cannot be relied

Table 1. The causes of death in beating heart organ donors during 1987 (Figures supplied by the United Kingdom Transplant Service)

Subarachnoid haemorrhage	215
Cerebrovascular accident	14
Intracerebral haemorrhage	120
Head injury (road traffic accident)	188
Head injury (other causes)	94
Road traffic accident (associated injuries)	59
Cardiac arrest	18
Brain tumour	13
Meningitis	10
Asthma	11
Asphyxia	11
Respiratory arrest (other causes)	3
Anoxia/hypoxia	17
Overdose	6
Others	36
Total	815

Table 2. Clinical criteria for diagnosing brain death in the United Kingdom

Known cause of irreversible and severe brain injury
Absence of hypothermia, electrolyte and endocrine abnormalities
No residual sedative drug effects
No pupillary response to light
Absent corneal reflex
Absent caloric responses
No motor response within distribution of cranial nerves
No gag or bronchial reflex
Apnoea in the presence of adequate PaCO ₂ (6.65 kPa/50 mmHg)

upon. The tests used to confirm brain death are summarised in Table 2 and must be repeated by the same two doctors. The exact timing of the second set will vary according to the clinical condition of the patient and may be up to 24 h from the first set. Inevitably some patients will become asystolic whilst the diagnosis is awaited but may be suitable for cadaveric organ donation if consent has been granted.

Prolonged elimination of drugs such as the benzodiazepines and opiates in critically ill patients is increasingly recognised [16–19]. The pharmacokinetic and pharmacodynamic effects of hypotension, hypothermia and endocrine failure on sedative and analgesic drugs has not been studied in the brain dead patient, but delayed drug elimination must be considered. In addition 6–10% of the population have been demonstrated to have pharmacogenetic abnormalities leading to delayed drug metabolism [20, 21]. The use of the specific opiate and benzodiazepine antagonists naloxone and flumazenil has been proposed as a test to exclude drug accumulation.

Improvement in conscious level, as shown by the return of reflexes or purposeful movements within the cranial distribution, after the administration of these antagonists disproves brain death. Conversely, with the lack of current clinical information, no improvement cannot guarantee lack of residual sedative effects. If there is doubt about the presence of sedative drugs then the diagnosis of brain death cannot be made.

Adverse effects of the two antagonists on haemodynamics and intracranial pressure make their use in the brain injured patient dangerous [22, 23]. If they are to be used then this should be postponed until all other tests have demonstrated brain death. A peripheral nerve stimulator should be used if the patient has renal failure and muscle relaxants have been used to exclude prolonged myoneural blockade.

Ventral pontine infarction ("the locked in syndrome"), idiopathic polyneuritis (Guillain-Barre syndrome), and brain stem encephalitis have been listed as conditions mimicking brain death [24]. The "locked in syndrome" is characterised by retained consciousness,

spontaneous respiration and vertical eye movements [25]. Polyneuritis has a characteristic history and presentation, consciousness is not lost although all muscle groups may be paralysed. Brain stem encephalitis is characterised by rousable stupor and retained purposeful limb movements [26]. All these conditions differ from the common causes of brain death (traumatic head injury, intracranial haemorrhage and cerebral hypoxia) in that they lack a defined severe cerebral injury as stipulated in the criteria. Furthermore, if a careful clinical examination is performed patients with these conditions will not fulfill the criteria either.

Time of death in the UK is legally defined as the time when the second set of tests has confirmed brain death. Details of testing are best documented on a single form, variations of which are available in many hospitals.

Consent to organ donation

Consent may have been granted before death occurred and this will usually have been recorded on a donor card. If the patient carried a donor card there is no legal requirement to discuss consent with the relatives but it is usual and recommended practice to do so. Alternatively permission may be obtained from relatives. This is best discussed with them after the first set of tests has been performed. Waiting until after the second set of tests has been completed can result in unnecessary distress for the relatives and delay in obtaining the organs. When brain death and organ donation are being discussed with relatives the concept of the beating heart donor should be clearly explained. This will avoid the possibility of future distress should the media highlight the issue at a later date.

If there are no relatives, the Hospital Administrator (as the legal possessor of the body) may grant permission to donate organs. Where the nature of the patient's death requires statutory reporting, the consent of the Coroner, Procurator Fiscal or Medical Examiner may need to be obtained. This should also be sought after the first set of tests to avoid later delays.

Both good and bad publicity have surrounded the practice of organ donation leading to fluctuations in supply but there is still a large deficit of donor organs. Many people wish their organs to be donated after death but may not communicate this to their next of kin. In The UK an "opting in" system is practiced in the form of widely available donor cards. These were at one time issued as part of the driving license. This latter practice has been withdrawn to comply with European Economic Community (EEC) regulations. Donor cards have not been successful due to low acceptance rates by the public or the cards not being carried or lost at the time of accident or hospital admission.

"Opting out" procedures have been implemented in some countries where the individual have to register on a central computer that they do not wish to donate organs.

"Required request" has been introduced as federal law in many states in the USA [27, 28] but there is no scientific evidence that the supply of donors has increased as a result. This legislation requires that the physician looking after a potential organ donor discusses the possibility of organ donation with the relatives. A compromise has been suggested in the form of "required discussion" where physicians must discuss potential donors with the local transplant team who could then approach the relatives [6].

At present in the UK it is usually a senior member of the medical team looking after the patient who asks for consent. They should have previously met the relatives and discussed the poor prognosis. The majority of relatives will gain some comfort out of the act of donating organs and this provides some relief from an otherwise tragic situation [29], some may even feel aggrieved if not approached about donation. A voluntary group "BODY" (British Organ Donor Society¹) has recently been set up in the UK to offer help to relatives in these situations. Transplantation programmes are more successful in children than adults but are hampered by the lack of donors in children under five years. Children may cause particularly strong emotions both in favour and against organ donation.

Organ retrieval

The UK Transplant Service (UKTS) in Bristol maintains a computerised record of all patients in need of organ transplantation and acts as a coordinating centre for the use of organs. Local organisation of the surgical organ retrieval is performed by regional transplant coordinators. The different organs retrieved from a single donor may be used in several different centres around the UK. Organs are also exchanged throughout the EEC. Within Europe there are a number of different coordinating organisations including Eurotransplant (the Benelux countries, FRG and Austria), France-Transplant, Scandia Transplant, Swiss Transplant, North Italy Transplant, Barcelona Transplant and Luso Transplant (Portugal). The activities of these organisations have been reviewed in depth [30].

Unavoidable delays at the transplantation centre may be seen as procrastination by the donor hospital and may lead to frustration. These delays may be caused by the difficulties in organising several retrieval teams simultaneously and the frequent shortage of

¹ "BODY", Balsham, Cambridge CB1 6DL, England, Tel.: (0223) 893636

ment. Screening for hepatitis and HIV is routinely performed in potential donors. However, using currently available assays, seroconversion occurs several weeks after primary infection. Antibody titres against HIV may be diluted by massive blood transfusion and blood products may themselves transmit infection to the donor. Testing the blood samples originally sent to the transfusion laboratory for crossmatching when the patient was first admitted may be helpful in such cases. Thus tests failing to demonstrate antibodies to HIV in donors cannot exclude HIV infection. Both HIV [32] and Hepatitis B [33] have been transmitted via transplanted organs and are likely to run a fulminant course in the immunosuppressed patient.

Cytomegalovirus and toxoplasmosis gondii both exist in latent forms in the normal population and may be reactivated in the immunosuppressed patient, particularly in the presence of other infections [34–36]. Both organisms may be transmitted to seronegative recipients via infected donor organs or blood transfusions and subsequently cause a primary infection. In the immunosuppressed patient both organisms may give rise to life threatening infections. Heart and heart/lung recipients appear particularly at risk from these organisms; some transplant units routinely screen all donor organs for them and then avoid giving seronegative recipients seropositive organs or blood [37]. Pyrimethamine may be given prophylactically to prevent toxoplasmosis gondii infection in mismatched donors [38].

Donor maintenance

After the criteria for brain stem death have been satisfied and consent obtained, patient care becomes donor maintenance and there is a change in emphasis from cerebral to donor organ protection. Failure to ensure that the organs are in optimal condition on removal may result in graft failure or malfunction in the recipient. Special problems arise when managing these donors, due to the nature of the severe intracerebral damage and resultant disturbances of cardiovascular function, temperature regulation and diabetes insipidus.

The cardiovascular system

Hypotension is a common finding in the brain dead patient. The vasomotor centre is damaged in common with the rest of the brain stem resulting in progressive vasodilatation. Dehydration from fluid restriction and diuretic administration is a recognised treatment for cerebral oedema and may result in hypovolemia. Myocardial function has also been shown to deteriorate in the brain dead baboon with increasing anaerobic me-

tabolism [39]. Bradycardias are common in the presence of severe cerebral injury due to loss of sympathetic drive. The destruction of the nucleus ambiguus in the brainstem abolishes resting vagal tone, therefore atropine fails to reverse bradycardia in this situation and this has been used as a diagnostic test for brain stem death [40, 41]. Bradycardias continue to respond to sympathomimetic drugs which act directly on beta-adrenergic receptors in the heart such as isoprenaline.

The first step in the correction of hypotension is to expand the intravascular volume using the measurement of central venous pressure (CVP) as a guide to adequate replacement. Urine output and core to peripheral temperature gradients are additional useful guides in this situation. Blood losses should be replaced with whole blood or packed cells to maintain a haematocrit of 30%. This haematocrit maximises oxygen supply by optimising the balance between oxygen transport by the red blood cell mass and blood flow related to changes in viscosity [42]. The choice of other fluids for the correction of hypovolaemia is controversial, particularly when large volumes need to be given quickly to resuscitate a hypotensive donor. At this centre a modified gelatin solution is used but it remains to be determined whether crystalloid or colloid solutions are better in this situation. If a low blood pressure persists after correction of hypovolaemia the circulation may be supported by infusion of an inotropic agent. Dopamine is currently the most popular drug because it causes renovascular dilatation at doses up to 5 µg/kg/min. Higher doses of it and other inotropes lead to progressive renal and systemic vasoconstriction. Drugs with predominantly vasoconstrictor properties (eg. aramine, ephedrine, metaraminol) should only rarely be required if the above steps are followed. Their inappropriate use may cause splanchnic vasoconstriction reducing liver and kidney perfusion. With worsening brain damage it may well become impossible to maintain an adequate circulation [4]. The blood pressure should not be considered in isolation, as a maximally vasodilated circulation may provide good organ perfusion despite low measured blood pressures.

Fluid balance

Fluid restriction and diuretic therapy are routine practice in many units looking after acute neurological injuries. Diabetes insipidus, glycosuria (due to steroid therapy), and hyperthermia (before brain death) are also common and increase water losses. When assessing organ donors, fluid intake and losses should be calculated for the previous period of intensive care. Clinical assessment of skin turgor and mucous membrane hydration, together with measurement of

peripheral temperature, urine output and central venous pressure and the laboratory estimation of plasma urea and electrolytes and haematocrit guide fluid replacement.

The urinary losses in diabetes insipidus should be replaced by 5% dextrose with added potassium [43] or preferably with a solution based on the measured urinary losses of electrolytes. The inappropriate use of 0.9% sodium chloride or plasma expanders containing 0.9% sodium chloride over a period of days may lead to progressive hyponatraemia.

Temperature control

Extensive damage to the brain stem causes loss of the normal central control of body temperature, the body effectively becoming poikilothermic. Without control of the temperature by passive warming the donor temperature will fall to that of its environment. Hypothermia is harmful as it causes progressive vasoconstriction and cardiac instability as the core temperature falls. Monitoring of body core temperature should be carried out and steps taken to conserve heat. Intravenous blood and fluids should be warmed, inspired gases should be heated and humidified, the donor should be placed on a warming mattress and covered by reflective insulating blankets.

Endocrine failure

The incidence of posterior pituitary failure manifest by diabetes insipidus is high in brain death [44]. Autopsy findings in such cases have shown necrosis, infarction or oedema of the pituitary as a consequence of the initial injury [44]. Polyuria results from lack of antidiuretic hormone with excretion of large volumes of dilute urine and this needs to be replaced on an hourly basis if marked fluid depletion is not to occur. Fluid therapy is discussed elsewhere in the text. A diuresis greater than 150 ml/h in an adult can be controlled using vasopressin or its synthetic analogues. Early use of vasopressin considerably simplifies the fluid management of these patients. Vasopressin may be effectively given as intramuscular injections or a low dose infusion of 1–2 units per hour [45]. The synthetic form dDAVP is more potent as an antidiuretic, has a longer duration of action and has less vasoconstrictor properties.

It would be surprising if anterior pituitary function was not damaged in a similar fashion to posterior pituitary function when brain death occurs and this has been confirmed experimentally in animals with brain stem injury [39]. Studies in humans have been less clear. Hall et al. [46] measured thyrotrophic hormone, prolactin and cortisol in 5 patients with brain death and could demonstrate no abnormality ex-

cept loss of the diurnal cortisol variation. Novitsky et al. [47] measured triiodothyronine (T₃), insulin and cortisol in 21 brain dead patients and found a decreased T₃ and a low normal cortisol and insulin concentration. On the basis of this and their animal work they gave T₃, cortisol and insulin to all their subsequent organ donors and appeared to have less cardiovascular and metabolic problems in them, compared to historical controls who did not receive hormone therapy. This study was both uncontrolled and retrospective with the attendant methodological problems but does indicate the need for further studies in this area.

Protection of organ function

In addition to the maintenance of adequate blood pressure, cardiac output and the avoidance of vasoconstriction specific protective treatments for individual organs are used. Renal protection is thought to be aided by low dose dopamine (2 µg/kg/min), mannitol infusions and frusemide (10 mg intravenous boluses). Most transplantation units give mannitol as a bolus of 20 g over 30 min immediately before kidney removal. Adequate flushing of kidneys before removal is important to wash out residual red cells. Handling of the renal vessels during donor nephrectomy may precipitate vascular spasm. This spasm has been reduced in experimental models by the administration of chlorpromazine, phenoxybenzamine, phentolamine, verapamil and prostaglandins [48]. There is a lack of comparative clinical studies for all these treatments and little information regarding other organs like the heart and liver.

There have been major advances in artificial organ preservation fluids for use immediately before organ removal and afterwards during storage. Many are still being investigated with different units using varied solutions. All are based on cold solutions, containing sugars as an impermeant and usually having a high potassium content. Together these reduce cellular swelling and metabolism. There has also been considerable interest in continuous hypothermic perfusion of organs *in vitro*. These topics have been reviewed in depth elsewhere [48, 49].

Ventilatory support

Continued artificial ventilation is necessary in the organ donor. The ventilator should be adjusted to give a PaCO₂ of 5.3–5.6 kPa and added oxygen given to maintain PaO₂ greater than 10 kPa. Oxygenation may be a problem if aspiration of stomach contents, acute lung injury, neurogenic pulmonary oedema or traumatic damage have occurred and arterial blood gases should be measured frequently. Positive end ex-

piratory pressure (PEEP) should not be used unless there are problems with oxygenation not responsive to increases in inspired oxygen concentration. PEEP increases mean intrathoracic pressure leading to decreases in thoracic venous return and a fall in cardiac output and renal blood flow. Other humoral mechanisms including release of antidiuretic hormone (ADH) and activation of the renin/angiotensin/aldosterone system have also been implicated [50]. PEEP should be avoided in the presence of haemodynamic instability and when not indicated specifically to improve PaO_2 . Carbon dioxide production is low in the absence of cerebral blood flow, sympathetic drive and muscle tone [51, 52]. Low minute volumes or the addition of a dead space to the ventilator circuit may be necessary to maintain normocapnia.

Lung transplantation requires special consideration. Oxygen at unnecessarily high concentrations (greater than 60%) should be avoided due to the risk of pulmonary oxygen toxicity. Low pressures of PEEP (5 cm water) are routinely used in these cases to preserve lung volume by preventing alveolar collapse. Salt and water overload must be avoided. The lungs must not become infected and "aseptic techniques" of tracheal suctioning continued.

The donor operation

Reflex movements, particularly in the limbs, may occur following stimuli in the presence of brain death. The intact lower spinal cord retains certain spinal reflexes which may give rise to muscle spasms and twitches on stimulation. Superficial reflexes are more common than deep muscle reflexes [53]. No reflexes occur in the distribution of the cranial nerves. Anxieties may arise as to the validity of brain stem death criteria, unless these changes are anticipated and understood by the attending staff. True decerebrate or decorticate posturing implies intact pathways within the brain and is not seen in brain stem death. Tachycardia and hypertension may also occur after surgical incision. The neuronal pathways for these haemodynamic responses are not clear but may reflect a spinal vasoconstrictor response or a humoral mechanism such as adrenal medullary stimulation by a spinal reflex [54].

Tubocurarine is often recommended for abolishing muscle movement but usually causes a drop in blood pressure due to histamine release and ganglionic blockade. Pancuronium or vecuronium, more cardiostable muscle relaxants are a better choice, given the high incidence of hypotension in donors.

The question of the use of analgesic and anaesthetic agents is difficult. Their use depresses the possibly harmful tachycardia and hypertension related to

surgical incision, otherwise their use is illogical in a brain stem dead donor. Nevertheless they are used by some experienced anaesthetists. The addition of volatile anaesthetic agents, in anaesthetic concentrations, to the inspired gases, overcomes some of the objections to organ donation expressed by some clinicians but others would regard this as an illogical position (D. Hill, personal communication). Most anaesthetists continue to use nitrous oxide as a carrier gas to avoid the administration of 100% oxygen from anaesthetic machines without a supply of compressed air.

Exact operative details differ between centres [55] and the procedure described is that used at this centre [56]. If all transplantable organs are to be removed the chest and abdomen are opened with a long midline incision from the jugular notch to the symphysis pubis. After a thorough inspection to exclude an unsuspected disease all organs are dissected out until attached only by their vascular pedicles. This dissection may take up to three hours, the most frequent delay being due to the presence of accessory vessels. The liver is dissected first followed by kidneys and pancreas.

When dissection is completed heparin is given intravenously to avoid coagulation around perfusion cannulae (15,000 units in an adult). Cannulae are then placed in the lower abdominal aorta, the inferior vena cava, and the portal vein in preparation for cold perfusion of the abdominal organs. The heart is perfused first with cold cardioplegic solution via a cannula in the aorta and fluid is vented by incising the superior pulmonary vein. Artificial ventilation is then discontinued. The liver is then perfused with ice-cold Ringer's lactate followed by 4.5% albumin solution. The kidneys are perfused with ice-cold Marshall's hypertonic citrate solution.

After cold perfusion the organs are removed and put in sterile bags and transported packed in ice to the recipient. Kidneys may be stored for up to 48 h (although organ survival after 72–96 h has been documented), livers up to 10 h, and heart and heart/lungs 4 h using these techniques. However, recent advances in preservation fluids may allow longer times in the future. Successful organ retrieval requires close cooperation between the different surgical teams from different centres. Efforts are being made in some areas to organise and train one surgical team to remove all organs rather than different teams each removing one organ.

Losses of fluids by bleeding and evaporation from an open abdomen and chest during the dissection phase are significant. Blood transfusion may be required during this dissection phase and blood should be crossmatched in anticipation.

Hypothermia may be a problem in the operating theatre when the donor has an open chest and abdo-

men. Open body cavities give rise to large heat losses from evaporation and radiation. Heat losses should be minimised by a warm theatre, warming all infused fluids, using heated humidifiers on ventilator circuits and using warming blankets beneath the donor.

Conclusions

The demand for organ donors is likely to increase each year and is likely to outstrip available supplies in the foreseeable future. Every effort should be made both to encourage organ donation and when offered, the donor organs should be kept in the best possible condition. This will mean allocation of medical and nursing time, plus resources similar to that given to other intensive care patients. Further studies need to be performed to identify all the consequences that result from brain death, in order that these may be corrected before organ removal.

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Brain stem death and organ donation

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Abstract

Organs for donation are in short supply in the United Kingdom, resulting in allegations that relatives of potential donors are not being asked for consent. Legislation on "required request" has been proposed to overcome this. The incidence, causes, complications, and patterns of organ donation in brain stem dead patients in one referral centre were studied over 12 months. Data were collected on all patients fulfilling criteria for brain stem death or considered suitable for donating organs after circulatory arrest. Forty two patients fulfilled the criteria for brain stem death, and in 10 further patients circulatory arrest occurred before formal testing was finished. The major causes of brain stem death were head injury (28) and intracranial haemorrhage (17). Consent to organ donation was obtained for 24 potential donors, and organs were donated by 23 of them. Twenty nine patients did not donate organs. The commonest reasons for failure to donate were medical unsuitability (13) and the coroner not releasing the body (eight). Consent was not sought in three cases, and the relatives refused consent in the remaining five.

This study suggests that required request will not considerably increase the supply of donor organs.

Introduction

Transplant surgeons have alleged that organs from many potential donors are not made available because of the reluctance of doctors to ask relatives to consent to donation and have therefore called for new legislation requiring clinicians to ask for consent.¹ This assertion, however, was made without knowledge of the true incidence of brain stem death, the number of cases of brain stem death in which donation is possible, or how often the question of organ donation is raised and consent is refused. The often misquoted figure of 4000 potential donors a year in the United Kingdom was published in 1981² but reported the number of patients in whom brain stem death was a possible diagnosis, not the number of organ donors.

The transplant teams at Addenbrooke's and nearby Papworth Hospitals are pioneers in organ transplantation. This generates much interest in the local and national media. Awareness of transplantation is thus high in the local population and the medical and nursing staff. It might therefore be expected that consent for organ donation would be considered by both medical staff and relatives more readily than in other centres. To determine the causes and complications of brain stem death in a major teaching hospital and to investigate whether required request would make an important difference to the numbers of potential donors failing to donate organs we prospectively studied for one year all patients admitted to the four intensive care units (general, paediatric, neurosurgical, and neurotrauma) at this hospital who were declared brain stem dead or considered suitable to donate organs after circulatory arrest.

Subjects and methods

From 18 November 1987 to 17 November 1988 all cases of brain stem death that occurred were reported

to us. At diagnosis of brain stem death the following information was collected: age, general diagnosis, duration of artificial ventilation in the intensive care unit after the declaration of death, and number and type of organs donated. If organs were not donated by a potential donor then the reasons for this were examined and allocated to one of four categories: medical contraindications, consent not requested, consent denied by relatives, and consent denied by the coroner. In addition, any complications directly attributable to brain stem death were recorded. These included hypotension (systolic blood pressure <80 mm Hg without inotropic support), diabetes insipidus (urine output greater than 200 ml/h in patients not receiving diuretics and without other causes of polyuria), and hypothermia (temperature less than 35°C without warming).

Results

Forty two patients (25 male and 17 female) fulfilled the criteria for the diagnosis of brain stem death during the period of study.³ In 10 other patients (three male and seven female) circulatory arrest occurred before formal testing could be completed. The mean (SD) age of the subjects was 37.3 (22.4) years (range 0.5-89 years), and the mean duration of artificial ventilation after testing was 123 minutes (range 10-3070 minutes). The large range in duration of ventilatory support reflects the need in one instance to wait until relatives arrived from the Far East to give consent. The major causes of brain stem death were head injury (28 cases) and spontaneous intracranial haemorrhage (17 cases), with intracranial tumour, hypoxic brain injury, and hydrocephalus the remaining diagnoses (table I). All 52 subjects had at least one complication of brain stem dysfunction, with diabetes insipidus and hypotension occurring in most (table II).

Consent to organ donation was obtained for 24 of the potential donors, with organs being donated by 23. One subject was found to have peritonitis at operation, which precluded organ retrieval. In four cases consent was restricted to donation of corneas, leaving 19 donors of solid organs, three of whom had had circulatory arrest. Table III shows the number of organs donated compared with the number for which consent to removal was granted. At the donor operation one kidney was found to have been traumatised previously and was not removed. Lack of a suitable recipient prevented the removal of a pair of kidneys, a liver, and three hearts. Three livers were not used because of a shortage of intensive care facilities for the recipients.

TABLE III—Number and type of organs donated by 19 donors compared with number of organs for which consent to removal given. In four further cases consent was restricted to corneal donation

Organ	Consented	Donated	Not used
Kidneys	38	35	3
Liver	16*	9	6
Liver-pancreas		1	
Heart	16*	7	7
Heart-lung		2	
Total	70	54	16

*Donor cannot donate liver and liver-pancreas or heart and heart-lung separately.

TABLE I—Causes of fatal brain injury in 52 potential organ donors

Cause	No of cases
Road traffic accident	20
Assault	5
Other trauma	3
Subarachnoid haemorrhage	8
Intracerebral haemorrhage	9
Cerebral neoplasm	3
Hypoxic brain injury	3
Hydrocephalus	1

TABLE II—Complications of fatal brain injury in 52 potential organ donors*

Complication	No of cases
Diabetes insipidus	34
Hypotension	33
Hypothermia	12
Oliguria	9
Pulmonary oedema	2

*More than one complication occurred in 22 cases.

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TABLE IV—Causes of failure to donate for 29 potential organ donors

Cause of failure	No of cases
Medical:	
Hypotension	8
Sepsis	2
Renal failure	2
Organ trauma	1
Consent:	
Denied by coroner	8
Denied by relative	5
Not requested	3

The age criteria for donations prevented the use of two livers and four hearts.

Twenty nine subjects failed to donate any organs (table IV). This was due to medical contraindications in 13 (profound hypotension, sepsis, trauma, or renal failure). In eight cases the injuries leading to brain stem death resulted in serious criminal charges being brought against another person. In such circumstances the coroner felt unable to grant permission for organ donation. There were five cases in which the relatives refused permission: in three they thought that the patient had "been through enough," in one the patient had expressed a wish not to donate organs, and in one the relatives had doubts about donation. Consent was not requested in only three.

Discussion

The shortage of organs for transplantation has been highlighted recently, accompanied by calls for changes in the law on consent to donation.¹⁴ In our study, though solid organs were donated from only 19 of 52 patients with brain stem death, in only three of the remaining 33 cases was consent for donation not requested. We suggest that failure to request donation after brain stem death is uncommon at our hospital. If this level of requesting donation is representative of that at most other centres then legislation to make request compulsory would not considerably increase the number of organs available for transplantation. Wakeford and Stepney, in a survey of attitudes to organ donation, concluded that coercive measures were less likely to increase the supply of donor organs than improved education of the public and the medical profession.⁵

Sixteen organs were not used when consent to their

removal had been granted because of lack of intensive care facilities or shortage of recipients matched for blood group and presence of cytomegalovirus. In this series organs from eight potential donors could not be used because the coroner would not release the body, a feature others have experienced with the procurator fiscal in Scotland (J D Miller, personal communication). The prevalence of traumatic causes of brain stem death suggests that this is a nationwide feature and is unlikely to change, though individual coroners and procurators fiscal have widely differing opinions on this subject, some releasing bodies when others would not.

Of concern is the large proportion (a quarter) of potential donors whose poor general condition rendered them unsuitable for donation. This, coupled with the high incidence of complications, means that such patients require careful medical and nursing care with particular attention to cardiovascular function. Perhaps by attention to these factors not only would absolute numbers of donors increase but there would also be an improvement in the condition of organs that are donated.

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Mortality during intensive care after orthotopic liver transplantation

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Summary

The postoperative course of 335 adult patients who underwent orthotopic liver transplantation from 1968-1987 was reviewed retrospectively to identify patients who died in the intensive care unit and the causes of death. Forty-four percent of all deaths occurred in the intensive care unit. The mortality rate in the intensive care unit peaked in 1984 (48%), but decreased to 11% in 1987. The main causes for death in the intensive care unit were infection (55%) and haemorrhage (19%). The patients who died spent more time in the intensive care unit, had a longer period of tracheal intubation and received a larger intra-operative blood transfusion than patients who died in other locations.

Key words

Surgery; Transplantation.
Complications; death.

Orthotopic liver transplantation (OLT) was pioneered originally in the United States by Moore¹ and Starzl.² The first orthotopic liver transplant in man was performed by Starzl in 1963. The operation was first performed in the United Kingdom by Calne in 1968. It is now accepted as a therapeutic modality in end-stage liver disease, acute hepatic failure, inborn errors of metabolism and some liver tumours.³

Liver transplantation has been performed for 20 years in the joint programme between Cambridge and King's College Hospital. This retrospective analysis of the experience in the Cambridge/King's College series attempts to identify the major causes of mortality of patients during their stay in the intensive care unit and to provide information on the changing patterns of problems which have contributed to mortality.

Patients and methods

Three hundred and thirty-five adult patients (over 14 years of age) have had at least one liver transplant in the Cambridge/King's College Hospital series during the period from 1968 to the end of October 1987. These patients were grouped according to a chronological scheme: 41 patients from 1968-1975; 60 patients from

1976-1980; 45 patients from 1981-1983; and 27-60 patients from each of the years 1984 to 1987. These groups were chosen as being of comparable size. The numbers in the groups from 1984 onwards represent a major increase in transplant activity in this hospital. Paediatric liver transplantation (now an increasing part of our practice) is not included in this study.

Indications for transplantation include chronic advanced hepatobiliary disease (CAHD) (biliary cirrhosis, chronic active hepatitis, alcoholic cirrhosis, cryptogenic cirrhosis and sclerosing cholangitis), acute liver failure (viral infection or poisoning), hepatic malignancy, inborn errors of metabolism (Wilson's Disease, alpha-1-antitrypsin deficiency, oxalosis) and the Budd Chiari syndrome. Surgical, anaesthetic and medical management is described in detail elsewhere.⁴

The place of death, time between operation and death, number of re-operations (if any), intra-operative blood transfusion, duration of stay in the intensive care unit (ICU) and the time of tracheal intubation were recorded for all patients who died. In the early part of the series intensive care measures such as artificial ventilation, tracheal intubation, catecholamine infusion and invasive monitoring were practised outside the ICU but, for statistical purposes, these patients are considered as if they had

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Table 1. Number (percentage of group) of deaths that occurred in the intensive care unit after orthotopic liver transplantation in seven time periods.

	1968-75	1976-80	1981-83	1984	1985	1986	1987
Number of patients	41	60	45	27	45	57	60
Age, years (SD)	41.2 (12.8)	40.4 (12.2)	39.7 (12.5)	37.4 (13.5)	40.5 (10.3)	41.4 (10.8)	39.8 (12.2)
Deaths in ICU (first admission)	9 (21%)	8 (13%)	12 (27%)	7 (26%)	6 (13%)	7 (12%)	5 (8%)
Deaths in ICU (readmission)	4 (10%)	5 (8%)	8 (18%)	6 (22%)	4 (9%)	3 (5%)	2 (3%)
Deaths in ICU (Total)	13 (31%)	13 (21%)	20 (45%)	13 (48%)	10 (22%)	10 (17%)	7 (11%)

received this therapy and died in the ICU. The main cause of death was obtained from the postmortem results (when available) or clinical data according to criteria used previously.⁵ When possible, only one (the major) cause of death was identified for each patient. Multisystem organ failure (MOF) was recorded as a cause of death when failure of two or more major organ systems was present. There are predominantly three causes of multisystem organ failure in this group of patients; infection, or infarction, or rejection of the donor liver. Infection was coded as the cause of death if there was microbiological confirmation of an organism (culture or serology). Infarction of the liver is characterised by a marked increase in the serum concentrations of transaminases and prothrombin time and by sudden deterioration in the patient's condition. Rejection can be diagnosed histologically or by the response to pulsed bolus doses of steroids. Infection, infarction or rejection was coded as the primary cause of death if proven; multi-system organ failure was coded if no cause was identified. Renal failure was defined as the presence of a plasma creatinine concentration of $> 217 \mu\text{mol/litre}$ or if there was a need for haemodialysis or haemofiltration. All other concurrent pathology present at the time of death was coded as an associated diagnosis. Student's *t*-test for unpaired data was used for statistical analysis where applicable.

Results

The numbers of patients who underwent OLT in each time period are shown in Table 1. One hundred and ninety-five of the 335 patients who have received OLT have died, 86 of

them (44% of deaths) in the ICU. Table 1 also shows the numbers of patients who died in the ICU during either their first admission or on readmission. The age and gender of adult patients who underwent OLT did not change significantly during the study period although the number of orthotopic liver transplants performed each year has increased steadily, particularly since 1984. The mortality rates for both the first and subsequent ICU admissions have fallen significantly since 1984. The main indications for transplantation are shown in Table 2. Initially a large number of patients were transplanted for malignancy but this has now become an uncommon indication. Alcoholic cirrhosis had the lowest ICU mortality and Wilson's disease the highest although the small numbers prevent meaningful statistical analysis. The groups associated with the largest decreases in ICU mortality over the years are those with cryptogenic cirrhosis and malignancy.

The main causes of death are shown in Table 3. Infection has remained the most important cause of death (55%) with haemorrhage the next most common (19%). Associated causes of death are shown in Table 4. Multisystem failure and renal failure make up 60% of all contributory causes of death. Multisystem (which includes renal) failure became increasingly recognised in the period 1981-1983 as the commonest cause of death. During that period renal failure occurred in 45% of patients who died in the ICU, much more frequently than previously. The relationship of renal failure to ICU mortality and one-year survival can be seen from Figure 1. Many factors influence survival, but the development of renal failure in critically ill patients is associated with high mortality. The decreasing incidence of

Table 2. Primary diagnosis and mortality in the intensive care unit after orthotopic liver transplantation.

	1968-75			1976-80			1981-83			1984			1985			1986			1987		
	n	d	%	n	d	%	n	d	%	n	d	%	n	d	%	n	d	%	n	d	%
Biliary cirrhosis	3	1	(33)	14	3	(21)	16	9	(56)	7	5	(71)	7	3	(43)	19	4	(21)	16	2	(12)
Chronic active hepatitis	2	0	(0)	7	1	(14)	7	3	(43)	5	3	(60)	9	2	(22)	8	1	(12)	13	1	(8)
Alcoholic cirrhosis	1	0	(0)	3	0	(0)	1	0	(0)	1	0	(0)	1	0	(0)	1	0	(0)	5	1	(20)
Cryptogenic cirrhosis	5	2	(40)	5	2	(40)	3	1	(33)	2	1	(50)	3	1	(33)	6	1	(16)	5	0	(0)
Sclerosing cholangitis	—	—	—	2	0	(0)	2	2	(100)	—	—	—	4	1	(25)	4	0	(0)	4	1	(25)
Acute liver failure	—	—	—	—	—	—	—	—	—	3	1	(33)	1	0	(0)	5	2	(40)	6	0	(0)
Malignancy	29	10	(34)	21	4	(19)	11	3	(27)	6	1	(16)	13	1	(8)	5	0	(0)	5	1	(20)
Wilson's disease	—	—	—	—	—	—	1	0	(0)	1	1	(100)	2	1	(50)	1	0	(0)	1	1	(100)
Budd Chiari	—	—	—	5	2	(40)	3	1	(33)	2	1	(50)	3	0	(0)	3	1	(33)	1	0	(0)
Other	1	0	(0)	3	1	(33)	1	0	(0)	—	—	—	2	1	(50)	5	1	(20)	1	0	(0)

n, number of patients; d, ICU deaths.

Table 3. Main causes of death. Percentages refer to all deaths in that location in each time period.

	Deaths in ICU							Deaths outside ICU 1968-87*
	1968-75	1976-80	1981-83	1984	1985	1986	1987	
Rejection	—	—	—	—	—	—	—	9 (9%)
Infarction	2 (15%)	1 (8%)	1 (5%)	1 (8%)	1 (10%)	—	—	6 (6%)
Infection	8 (62%)	7 (54%)	11 (55%)	8 (62%)	4 (40%)	4 (40%)	5 (71%)	30 (29%)
Haemorrhage	—	3 (23%)	3 (15%)	2 (15%)	3 (30%)	4 (40%)	1 (14%)	1 (1%)
Multisystem failure	1 (8%)	1 (8%)	4 (20%)	2 (15%)	—	1 (10%)	—	—
Recurrence	1 (8%)	—	—	—	—	—	—	30 (29%)
Biliary anastomosis	—	—	—	—	—	—	—	3 (3%)
Pulmonary embolus	—	—	—	—	—	—	—	3 (3%)
Gastrointestinal haemorrhage	—	—	1 (5%)	—	—	—	—	2 (2%)
Cerebral haemorrhage	1 (8%)	1 (8%)	—	—	1 (10%)	1 (10%)	1 (14%)	—
Other	—	—	—	—	1 (10%)	—	—	10 (11%)
Unknown	—	—	—	—	—	—	—	7 (7%)

*Excluding theatre deaths.

Table 4. Associated causes of death in patients who died in ICU. Percentages are related to ICU deaths for that period.

	1968-75	1976-80	1981-83	1984	1985	1986	1987
Rejection	1 (8%)	—	—	—	—	—	—
Infarction	—	1 (8%)	—	—	1 (10%)	1 (10%)	—
Haemorrhage	—	—	1 (5%)	—	—	—	1 (14%)
Multisystem failure	1 (15%)	2 (15%)	14 (70%)	6 (46%)	3 (30%)	2 (20%)	2 (28%)
Biliary problems	1 (8%)	2 (15%)	1 (5%)	—	—	—	—
Pulmonary embolus	2 (15%)	1 (8%)	—	—	—	—	—
Gastrointestinal haemorrhage	—	—	—	—	1 (10%)	—	—
Cerebral haemorrhage	—	1 (8%)	—	—	—	—	—
Renal failure	1 (8%)	—	9 (45%)	3 (23%)	1 (10%)	1 (10%)	1 (14%)
Cardiac failure	—	—	—	—	1 (10%)	1 (10%)	—
Disseminated intravascular coagulation	—	—	—	1 (8%)	—	—	—
Mesenteric thrombosis	—	—	—	—	1 (10%)	—	—
Miscellaneous	1 (8%)	—	—	1 (8%)	—	1 (10%)	—

renal failure in this group appears to be associated with a decrease in ICU mortality (except for 1987) and an increase in one-year survival.

Table 5 presents further information on patients who died during admission to the ICU or after discharge. There is no statistically significant difference in age or gender. The average number of days spent in the ICU was shortest for patients who survived but there was no statistically significant difference in duration of ICU stay between patients

who died during their first ICU admission and those who died in their second ICU admission. Patients who died had a longer period of tracheal intubation and required more intra-operative blood transfusion. The incidences of the main causes of death for all patients are shown in Figure 2.

Discussion

The current one-year survival after OLT at this centre is 66%. This is higher than that reported by the European

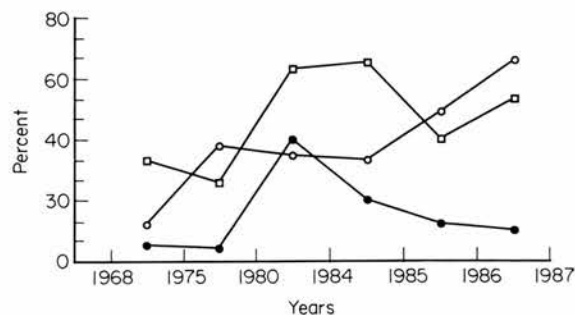


Fig. 1. The incidence of renal failure during the period of intensive care in patients who had undergone liver transplantation between 1968 and 1987. Mortality (as a percentage of all deaths) and one-year survival for the same period are shown also. —○—, one-year survival; —●—, renal failure; —□—, ICU deaths.

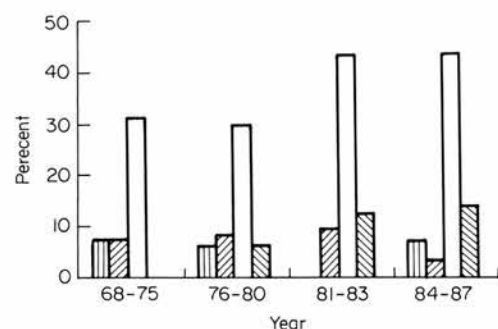


Fig. 2. Main causes of death after liver transplantation for the period 1968 to 1987. ▨, rejection; ▤, infarction; □, infection; ▩, haemorrhage.

Table 5. Risk factors associated with death after liver transplantation. Values are expressed as mean (SD).

	Deaths outside ICU (<i>n</i> = 81)*	Deaths during first admission to ICU (<i>n</i> = 49)	Deaths during readmission to ICU (<i>n</i> = 30)
Age	41 (12)	41 (10)	39 (12)
Sex	34 M, 47 F	25 M, 24 F	13 M, 17 F
Survival time (days)	350.7 (600.6)	11.6 (10.6)†	89.1 (136.2)†‡
ICU time (days)	6.1 (10.1)	11.6 (10.6)	10.9 (14.4)
Patient days	424	593	293
Intubation time (hours)	38.5 (78.9)	162.5 (200.4)†	124.2 (245.3)†
Intra-operative blood transfusion (litres)	8.1 (6.9)	19.6 (15.0)	9.8 (7.6)§
Total number of re-operations	43	34	16
Number of patients (% of total) re-operated	35 (43%)	24 (49%)	12 (40%)
ratio	1.2 : 1	1.5 : 1	1.3 : 1

*Excluding deaths in theatre.

†*p* < 0.01 (with respect to column 1).‡*p* < 0.01, §*p* < 0.05. (with respect to column 2).

Transplant Registry⁶ and compares well with other series.⁷⁻⁹ Survival has improved steadily from 12% during the first 8 years up to 49% in 1985 and 66% in 1986. The percentage of deaths that occurred in ICU increased from 31% in the initial period to 48% in 1984 but since that time it has fallen each year and was 11% in 1987.

Major changes in the management of these patients occurred during the study period. Postoperative artificial ventilation for the first 24 hours was introduced in 1976; prior to this period patients were extubated at the end of operation and allowed to breathe spontaneously.¹⁰

The period with the maximum incidence of multisystem organ failure including renal failure (1981-1984) coincides with the introduction of cyclosporin A, given immediately after OLT, into clinical practice. This high incidence of renal failure caused a change in our therapeutic regimen. Cyclosporin is now administered 48 hours after the end of operation when the patient is haemodynamically stable and has adequate renal function. Further research into renal protection led us to introduce low-dose dopamine infusion as part of routine management. This resulted in a reduced incidence of renal impairment and less need for haemodialysis.¹¹ These changes and other more general measures (see below) were associated with reductions in the incidence of renal failure in patients who died in the period from 1981-1983 (45%), to 23% in 1984 and 10% in 1986. Simultaneously the one-year survival rates increased to 49% and 66% in 1985 and 1986 respectively (Fig. 1).

The major cause of death in the ICU continues to be infection, an experience reported also by others.⁵ Its total incidence appears not to have changed with time; it remains the primary cause of death in 35-45% of all patients and contributes to 55% of all ICU deaths. The high incidence of infection is a reflection of the severity of pre-existing illness, the magnitude of the operation and the need for immunosuppression. Almost all of the deaths caused by haemorrhage, multisystem failure and cerebral problems occurred in the ICU. Half of the deaths associated with ischaemic damage to the donor organ occurred during the period of intensive care. No deaths attributed primarily to rejection, pulmonary embolism or biliary problems occurred in the ICU.

The volume of blood transfused intra-operatively appeared to be related closely to the ICU deaths that occurred early in the postoperative period (Table 5). The mean blood usage in patients who died in the ICU was 19.6 litres, more than reported by others;¹² this may reflect differences between the patient groups or techniques in the two centres. Periods of hypotension, residual peritoneal blood clot and tamponade of renal vessels by large amounts of blood¹³ may lead to an increased risk of renal failure and infection. Patients who died in a subsequent ICU admission also had a larger blood loss than survivors.

The durations of stay in the ICU and of tracheal intubation were, as might be expected, longer in the nonsurvivors (on average more than 10 days and 120 hours respectively).

Less quantifiable aspects of postoperative intensive care concern the adoption of a management protocol in 1984, subsequently revised annually. Medical and nurse staffing levels have also improved during this time. We have not attempted to analyse the effects of these developments but others have shown that outcome in an ICU with adequate numbers of trained staff is better than in a unit with low staff numbers.¹⁴ Other factors, not related directly to the intensive care these patients received, contributed also to the improved survival during the review period. Improvements in donor maintenance,¹⁵ organ preservation¹⁶ and antibiotic prophylaxis have occurred and there has been a change in the diagnostic groups transplanted. Originally a large number of patients were transplanted for malignancy. Unfortunately many of these patients developed recurrence of their tumour and it is not now a common indication for transplantation. Patients with malignancy are usually transplanted more rapidly than others with the result that they tend to be less unwell than those with end-stage liver disease and so pose fewer peri-operative problems, a feature demonstrated in their low overall mortality since 1975.

Eleven percent of patients died during the period of intensive care in 1987 despite improvements in management. Two major causes of mortality, infection and haemorrhage, require attention. It is of note that these have remained essentially unchanged during this period. Some of the deaths diagnosed as being related to infection may have

been caused by rejection and the fine balance between excessive immunosuppression which may result in infection and inadequate immunosuppression with a consequent increased risk of rejection requires careful management. Postoperative haemorrhage continues to be a problem and may represent a complication of surgery, derangement in the coagulation mechanism due to the pre-existing poor synthetic liver function or failure of synthetic function of the new liver.

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Postoperative analgesia for haemorrhoidectomy

A comparison between caudal and local infiltration

S. J. PRYN, M. M. CROSSE, M. S. C. MURISON AND F. P. MCGINN

Summary

This study compared the analgesic effectiveness of local infiltration of bupivacaine with caudal extradural bupivacaine in the first 48 hours after haemorrhoidectomy. Surgical and anaesthetic protocol was rigidly standardised. The caudal group had significantly less pain in the first 6 hours after haemorrhoidectomy, and on first bowel opening, when compared to those who received local infiltration of bupivacaine. There was no significant difference between the two groups with respect to further analgesic requirements, complications, time to first bowel action, and duration of hospital stay. The definite advantage of caudal extradural bupivacaine for haemorrhoidectomy must be balanced against the rare but potentially serious complications associated with its use.

Key words

*Pain; postoperative.
Anaesthetic technique; caudal.*

Haemorrhoidectomy has been described as agonisingly painful¹ and has unfavourable notoriety in this respect. However, there is evidence that caudal epidural analgesia offers patients some benefits.²⁻⁵ The study by Berstock³ showed that bupivacaine caudal analgesia dramatically reduces the postoperative opiate requirement (by 79%) and halves the time to first bowel action (from 4 to 2 days). Presumably the two are related, since opiate drugs tend to cause constipation.

Local infiltration of bupivacaine can also provide good operative anaesthesia for haemorrhoidectomy,^{6,7} and although to our knowledge there are no studies which demonstrate continued analgesia into the postoperative period, one can reasonably expect this to occur, since it does at other injection sites.⁸

Both methods of administration of bupivacaine are regularly used in our hospital to provide postoperative pain relief after haemorrhoidectomy. It is proposed that if the technique of local infiltration can be shown to be as effective as the already proven advantages of caudal analgesia, then this may be a safer, quicker and more reliable method. In addition, if one method provides superior analgesia compared to the other, then one might expect a greater opiate sparing effect, and hence a shorter time to bowel action and discharge from hospital. This would add the advantage of cheaper patient care.

Methods

Forty-four consecutive patients about to undergo elective haemorrhoidectomy under general anaesthesia by one of the two participating surgeons were randomly allocated into two groups of 22. Group 1 received caudal analgesia and Group 2 local infiltration analgesia with 0.25 ml/kg bupivacaine 0.5% as part of the anaesthetic technique. The only exclusion criteria were for those patients with specific contraindications to caudal extradural analgesia (e.g. coagulopathy, localised infection, pre-existing neurological deficit, patient refusal, and those with known hypersensitivity to local anaesthetic agents). All patients gave their informed consent before operation and approval for the study was obtained from the district ethics committee.

The surgical protocol was rigidly standardised. All patients had third-degree piles, or second-degree after failed Barron's band ligation, and they received an enema the day before surgery. The surgeon infiltrated around the haemorrhoids 0.25 ml/kg of a solution of either 1 in 200 000 adrenaline (Group 1), or bupivacaine 0.5% with 1 in 200 000 adrenaline (Group 2), after induction of general anaesthesia. Haemorrhoidectomy was performed by Milligan-Morgan ligation excision⁹ and the wound dressed with a Jelonet pack which was left in place until the next morning. The patients were treated with regular aperients

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Chlormethiazole sedation for critically ill patients in renal failure

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Summary

Chlormethiazole infusions were used successfully to provide night sedation for 10-19 nights in three patients with renal failure managed by continuous veno-venous haemofiltration with dialysis. Fluid overload has accompanied the use of this drug previously because of its low concentration. The ability to remove large amounts of fluid during haemofiltration dialysis proved to be effective in preventing this. All three patients had impaired liver function and showed evidence of chlormethiazole accumulation after 4-6 days. The combination of progressive reduction in dose and daily withdrawal of infusions prevented a major problem. Acceptance of this technique by the patients was high. Chlormethiazole may be a useful addition to the drugs available to provide sedation in well defined clinical circumstances.

Key words

*Hypnotics; chlormethiazole.
Kidney; failure.*

Infusions of chlormethiazole are well established in the management of alcohol withdrawal, status epilepticus, pre-eclampsia and short term sedation. The drug has been used also for prolonged infusion in critically ill patients,¹ in whom it can produce effective sedation and permit artificial ventilation whilst preserving cardiovascular stability. Modig² has suggested that chlormethiazole may have a protective effect in endotoxic shock, minimising cardiovascular and pulmonary instability, which could be advantageous in the critically ill patient.

Intravenous administration of chlormethiazole by bolus doses or by short infusions produces effective sedation with rapid onset and recovery due to redistribution into a large volume. It is eliminated mainly by hepatic metabolism, with less than 1% of unchanged drug excreted in the urine.³ Saturation of redistribution sites may occur during long term infusions; its effect then is terminated by metabolism alone.⁴ This problem may be exacerbated in the elderly,⁵ the critically ill¹ and in patients whose hepatic function is chronically impaired.⁶ Scott *et al.*¹ have suggested that the decrease in metabolism may be due to a reduction in hepatic blood flow. Thus recovery from long term infusions (more than 24-48 hours) may be prolonged significantly in some patients.

Chlormethiazole is formulated for intravenous use as a 0.8% solution in 4% glucose buffered with approximately 30 mmol sodium hydroxide to achieve a pH in the normal range. It is not available in a more concentrated form

because the incidence of venous thrombophlebitis is unacceptably high and it may produce haemolysis if concentrations of 5% or more are used.⁷ Thus, a large fluid load may be required if chlormethiazole is used for prolonged sedation. This feature has limited its usefulness, particularly in patients with renal failure and those with fluid and electrolyte problems.

Haemofiltration⁸ removes fluid and small molecular weight substances (approximate molecular weight < 20 000) and can remove large volumes of fluid. The patient's own blood pressure can be used to drive the blood around the circuit (continuous arteriovenous haemofiltration; CAVH) if arterial and venous lines are inserted. Alternatively, two venous lines with a blood pump can be used to circulate the blood (continuous veno-venous haemofiltration; CVVH). Large volumes of haemofiltrate may be removed and replaced with a suitable solution. Continuous arteriovenous haemofiltration with dialysis (CAVHD) combines low volume arteriovenous haemofiltration with continuous perfusion of the filter using a haemodialysis solution.⁹ Continuous veno-venous haemofiltration with dialysis (CVVHD), like CVVH, uses two venous lines and a blood pump, and provides a high and consistent flow through the membrane. These latter two techniques allow slow, gentle, continuous haemodialysis as well as control of fluid balance.

We describe three patients in whom CVVHD allowed the use of chlormethiazole.

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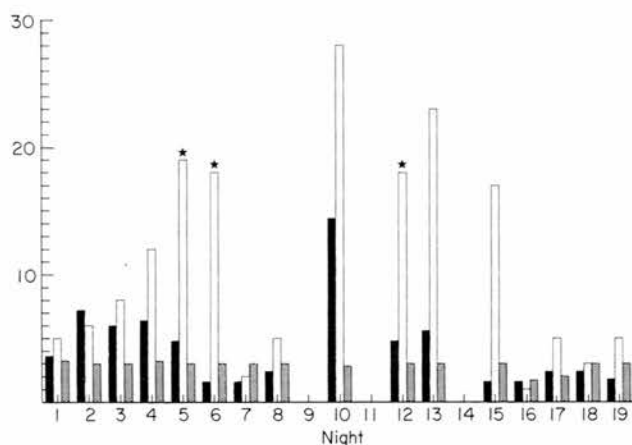


Fig. 1. Drug dose (mg), ■; recovery time (hours), □; sedation score, ▨; for 19 nightly chlormethiazole infusions in patient 1. *Marks the three occasions when patient 1 had not recovered noticeably before the infusion was inadvertently recommenced.

Case histories

The first patient, a 49-year-old male, had undergone orthotopic liver transplantation for cirrhosis due to α_1 -antitrypsin deficiency. This had been complicated by the development of acute lung injury and acute renal failure 12 days after operation. The second patient, a 62-year-old male, had undergone resection of an abdominal aortic aneurysm. Subsequently, the left femoral graft and mesenteric artery became occluded and this caused infarction of the large bowel. Acute renal failure developed 2 days after operation. The third patient, a 44-year-old female, had undergone orthotopic liver transplantation for primary biliary cirrhosis. The patient had deteriorating renal function before operation, due to the hepatorenal syndrome, and developed acute renal failure on the second day after operation. All three patients required continuous mandatory ventilation (CMV) or synchronised intermittent mandatory ventilation (SIMV) and CVVHD. Abnormal liver function, predominantly obstructive in nature, developed in patients 1 and 2. Patient 3 had abnormal liver function (primarily hepatocellular in nature) which improved significantly during the period of chlormethiazole infusions (see Table 1).

Each night, chlormethiazole infusions were given to the patients to facilitate sleep. Patient 1 received the drug from the 21st to the 39th day, patient 2 from the 13th to the 29th day and patient 3 from the 10th to the 19th day in the Intensive Care Unit. Previously, sedation had been with bolus doses of morphine and midazolam given when required, but this regimen proved difficult to control.

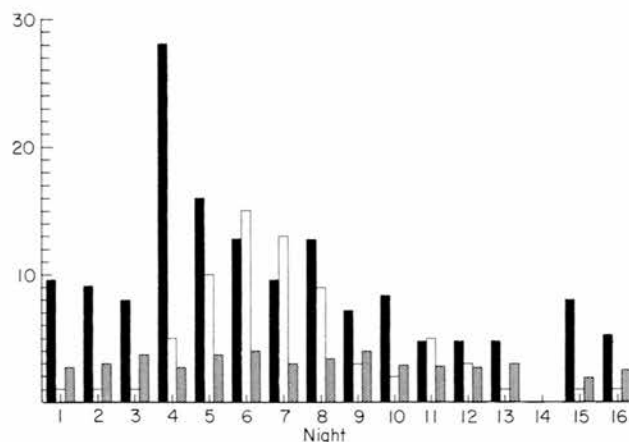


Fig. 2. Drug dose (mg), ■; recovery time (hours), □; sedation score, ▨; for 16 nightly chlormethiazole infusions in patient 2.

Propofol infusions were not used because we have observed that this method of sedation in deeply jaundiced patients may result in bradyarrhythmias (unpublished observation). The rate of the chlormethiazole infusions were controlled by the nursing staff within prescribed dose limits. The infusions were stopped during the day to encourage a normal circadian rhythm and to prevent drug accumulation. Sedation was assessed by the nursing staff each hour using the sedation score routinely employed in the intensive care unit:¹⁰ 1, fully alert; 2, roused by voice; 3, asleep; 4, roused by pain; 5, unrousable. This simple scoring system may lack the sensitivity of more complex systems but has proved effective and consistent in clinical use.

The following information was recorded for each infusion: the infusion rate; the total dose of chlormethiazole given; the average sedation score during the infusion; and the time taken for the patient to reach maximum awakening after termination of the infusion. Figures 1–3 show these data for the three patients.

Adequate night sedation was defined as a score of 2 or 3. This objective was not achieved on only two occasions in the total of 45 nightly infusions. However, excessive sedation (score more than 3) occurred on six occasions, and on three occasions patient 1 had not recovered noticeably before the infusion was inadvertently restarted (marked with * in Fig. 1). It was necessary to withhold sedation for patient 1 on three occasions, and on one occasion for patient 2, because of oversedation.

Recovery time increased rapidly after sedation on the first 6 nights in all patients and improved only when the drug dose was reduced (usually achieved by a decrease in the duration of the infusion to approximately 3 to 4 hours rather than a change in the rate of infusion). Recovery

Table 1. Range of liver function tests during the period of chlormethiazole infusion.

	Patients			Normal range
	1	2	3	
Bilirubin ($\mu\text{mol/litre}$)	240–466	15–55	45–97	2–17
Alkaline phosphatase (units/litre)	88–460	108–322	158–224	30–135
Alanine aminotransferase (units/litre)	28–51	19–48	33–203	7–40

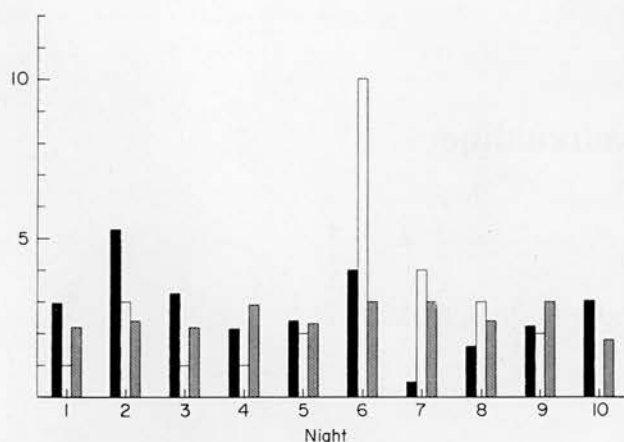


Fig. 3. Drug dose (mg), ■; recovery time (hours), □; sedation score, ▨; for 10 nightly chlormethiazole infusions in patient 3.

times decreased towards the end of the period of chlormethiazole infusions as experience was gained in administration of the appropriate dose of chlormethiazole, and the doses administered were considerably lower than during the first few days.

Large changes in heart rate or blood pressure were not seen. The maximum decreases in systolic arterial pressure were 20–25% of those before the chlormethiazole infusion and probably not much greater than those which occur during natural sleep. Chlormethiazole may cause an increase in heart rate of about 20–40 beats/minute¹ but we did not observe this.

No problems in fluid or electrolyte balance were encountered that were not controlled easily by CVVHD.

Discussion

At the present time there is no ideal sedative for long term use in critically ill patients. Chlormethiazole provides good sedation with relative cardiovascular stability but one of its major drawbacks has been the large fluid load associated with its administration. CAVH, and more recently CVVHD and CAVHD, are used increasingly in critically ill patients with renal failure, and these techniques can be used to solve the fluid balance problems.

Relatively large doses of chlormethiazole were needed during the first 4–6 days and these were associated with a rapid recovery time. This represents cessation of clinical effect by redistribution. However, as the redistribution sites became saturated, the recovery times increased dramatically as termination of effect became dependent on metabolism. The dose must be reduced to match this change if acceptable recovery times are to be achieved.

Recovery time decreased later in the study period. This may represent the development of tolerance described with morphine,¹¹ fentanyl¹² and midazolam (unpublished observation). Alternatively clearance may have been reduced initially due to poor liver function, but may have increased subsequently as hepatic function improved; this phenomenon was observed during sedation with midazolam.¹³

Chlormethiazole infusions provided effective nocturnal

sedation with cardiovascular stability over many nights in these three patients with renal failure. Once experience was gained with chlormethiazole, particularly in down-titration of the dose to avoid cumulation, it was found to be an effective and safe technique that provided smooth and consistent sedation in contrast to the previous difficulties experienced in providing adequate sedation with bolus doses of morphine and midazolam.

There is evidence from animal experiments that chlormethiazole might attenuate the cardiovascular and pulmonary instability associated with septic shock, which is a major cause of morbidity and mortality in the critically ill,² particularly in those with renal failure. This remains to be substantiated in man. Chlormethiazole may be used to provide both effective sedation and possibly prophylaxis against the adverse haemodynamic effects of sepsis. The relatively cheap price of chlormethiazole is a further advantage in the current climate of fiscal restraint.

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A plea for noradrenaline

M. E. STUART-TAYLOR AND M. M. CROSSE

Summary

Hypotension induced by nifedipine and chlorpromazine is discussed, together with the role of noradrenaline in the correction of this problem, which was resistant to other forms of therapy.

Key words

*Complications; hypotension.
Calcium channel blockers; nifedipine.*

Case history

A 52-year-old man was admitted for elective aortobifemoral bypass graft for occlusive vascular disease and was assessed 36 hours before surgery.

He had smoked 40 cigarettes per day for 40 years and had severe chronic obstructive airway disease, for which he received salbutamol and beclomethasone by inhaler. He was also prescribed bendrofluazide for hypertension. Psychiatrists were treating successfully with chlorpromazine a mixed psychiatric problem of schizophrenia and depression. He also took cimetidine and naftidrofuryl oxalate (praxiline). He had shortness of breath on exertion, with exercise tolerance limited to 0.25 mile on the flat, due to intermittent calf claudication. The ECG was normal.

The patient was found to have a blood pressure of 185/125 mmHg at the pre-operative assessment, but stated that he always became very hypertensive when admitted to hospital. However, the next day his blood pressure always returned to his usual level of 150/80. Examination of the records of his previous three admissions to hospital showed this statement to be correct. Instructions were therefore given for 4-hourly blood pressure measurements, no change in treatment, and, provided his blood pressure decreased to its usual level, surgery.

He was premedicated with temazepam 20 mg and metoclopramide 10 mg orally on the morning of surgery in addition to his normal medication. On arrival in the anaesthetic room his blood pressure was 150/95 mmHg. Peripheral venous, central venous and arterial lines were inserted under local anaesthetic. ECG, central venous (CVP) and arterial pressures were on continuous display and the

patient was anaesthetised with midazolam 3 mg, fentanyl 250 µg, and vecuronium 8 mg. The blood pressure decreased over several minutes to 110/75 mmHg. Tracheal intubation resulted in an increase in blood pressure to 160/95 mmHg. Anaesthesia was maintained with 67% nitrous oxide in oxygen and end-tidal CO₂ was kept within normal limits. Volatile anaesthetic agents were avoided in view of the expected α -adrenergic block by chlorpromazine. The patient's blood pressure decreased progressively to 85/55 mmHg over the next 10 to 15 minutes. There was no response to intravenous infusion or to skin incision and, as the patient's right heart filling pressure was adequate, a dopamine infusion was commenced via the central venous line to reverse the hypotension. The initial dose was rapidly increased to 25 µg/kg/minute with no effect on the blood pressure. Incremental doses of 1:10 000 adrenaline were given over the next 10 minutes to a total of 1 mg. There was no change in arterial blood pressure which remained between 60/40 and 80/50 and there was a mild increase in pulse rate to 85 beats/minute.

A rapid assessment of possible causes of hypotension was made; this included air embolism, myocardial infarction, tension pneumothorax, cardiac tamponade from insertion of the CVP line, incorrect medication administered, poor calibration of pressure monitors and anaphylaxis. The first six possible causes were considered unlikely. However, the patient did appear flushed and vasodilated with bounding pulse; and in view of a recently administered antibiotic, an allergic reaction was considered possible. Chlorpheniramine 10 mg was given intravenously. The surgeon cross-clamped the aorta at this stage which also had no effect on blood pressure. A review of the patient's

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EXTRAHEPATIC MORPHINE METABOLISM IN MAN DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION

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The primary site of morphine metabolism has been the subject of speculation [1, 2]. Historically it was assumed that the liver was the predominant organ involved in the metabolism of morphine, but the apparent sensitivity to morphine of patients in renal failure [3] suggested that the kidney might be a major alternative site. This study has examined the role of the liver in the metabolism of morphine in patients during the anhepatic phase of liver transplantation.

The operation of liver transplantation has been classified into several phases including dissection, anhepatic and reperfusion phases. During the dissection phase the diseased liver is "skeletonized" onto its vascular pedicles, namely the suprahepatic vena cava, the infrahepatic vena cava, the hepatic artery and portal vein, before removal. The anhepatic phase starts after clamping these vessels, following which the diseased liver is removed entirely. During this period, vessels of the donor liver are anastomosed to those of the recipient. When the anastomoses of the portal vein and inferior and superior venae cavae are completed the clamps are removed and the liver is reperfused with portal blood. Finally, the hepatic artery and biliary anastomoses are completed [4].

The altered physiology of the anhepatic period has been described previously [5]. The venous drainage of the lower half of the body and abdominal contents relies on the presence of collateral vessels which are present in the healthy human and increase markedly in the presence of

SUMMARY

The primary site for the metabolism of morphine has been the subject of controversy for some time. We studied morphine metabolism during the anhepatic phase of orthotopic liver transplantation in seven adult patients. After injection of morphine 10 mg at the beginning of this phase, the plasma and urinary concentrations of unchanged morphine, morphine-3-glucuronide, morphine-6-glucuronide and normorphine were measured by high pressure liquid chromatography. Small but measurable concentrations of morphine metabolites were found in the plasma and urine whilst there was no functional liver tissue in the body. Morphine metabolism increased markedly when the new donor liver was reperfused. This suggests that, in these patients, the liver is the primary site for metabolism of morphine.

portal hypertension. These venous collaterals provide a compromised venous return when the inferior vena cava is cross clamped. Although the perfusion of the kidneys and intestines is compromised, these patients usually produce 50-100 ml of urine during the anhepatic period. On reperfusion of the donor liver there is a large increase in venous return and improved circulation to the lower half of the body.

PATIENTS AND METHODS

We studied adult patients who were likely to have an uncomplicated intraoperative course. The study was approved by the Hospital Ethics Committee and written informed consent was obtained in all patients before operation.

With the exception of patients with small

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intrahepatic tumours, most patients undergoing liver transplantation have advanced liver disease with associated porto-systemic shunts and coagulation problems. Surgery may be technically difficult, with large blood loss. The patients in this series were chosen to have a low risk of this complication: those with good coagulation, lack of concurrent medical problems and no previous intra-abdominal surgery.

Anaesthesia was conducted as described previously [6]. Patients were premedicated with an oral benzodiazepine and anaesthesia was induced with thiopentone and maintained with nitrous oxide and isoflurane in oxygen. Neuromuscular block was provided with suxamethonium followed by an infusion of atracurium. Analgesia was provided by intermittent bolus injections of fentanyl. Dopamine $2 \mu\text{g kg}^{-1} \text{min}^{-1}$ and mannitol 10 g h^{-1} were infused to maintain urine output. Central and peripheral venous cannulae, a radial arterial cannula and urinary catheter were inserted as routine.

Baseline blood and urine samples were taken immediately before the anhepatic phase. Three minutes after the anhepatic phase had started, morphine 10 mg diluted in saline 10 ml was administered into a central vein; the delay was to allow acute haemodynamic changes to resolve. Blood samples were taken at 2, 5, 10, 15, 20, 30 and 40 min after injection and immediately before reperfusion. Urine samples were taken at 5 and 30 min and immediately before reperfusion.

On reperfusion the sampling was repeated, with blood and urine samples taken at the same times as during the anhepatic phase. Blood loss, blood replacement, urine output and body temperature were recorded for each stage. Blood samples were placed in lithium-heparin tubes, centrifuged at $3000 g$ for 5 min, and then separated into plain siliconized tubes with screw caps to minimize adsorption. Urine and plasma samples were stored at -20°C for later analysis of morphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and normorphine, using a method described previously [7, 8].

RESULTS

The details of the seven patients studied are shown in table I. All patients had significant hepatic dysfunction with the exception of patient No. 2 who had a solitary hepatoma. Table II lists some of the operative details of these patients.

TABLE I. Demographic data and presenting diagnosis of the seven patients

Patient No.	Age (yr)	Sex (M/F)	Weight (kg)	Presenting diagnosis
1	52	M	56	Primary biliary cirrhosis + hepatoma
2	41	M	70	Carcinoma of liver
3	35	M	77	Sclerosing cholangitis + cholangiocarcinoma
4	51	F	60	Primary biliary cirrhosis
5	29	F	60	Alcoholic cirrhosis
6	42	F	54	Chronic active hepatitis
7	52	M	60	Alcoholic cirrhosis + hepatoma

TABLE II. Operative details of the seven patients (mean (SEM))

Phase	Blood loss (ml)	Duration (min)	Urine volume (ml)
Dissection	1788 (1147)	135 (45)	345 (279)
Anhepatic	1657 (1029)	56 (9.4)	57 (47)
Reperfusion	2862 (2288)	95.7 (19.5)	282 (182)

Although large by general surgical standards, blood loss was not excessive for this operation. All patients produced urine during the anhepatic period. The mean cold ischaemic time, defined as the period of cold storage of the livers before transplantation, was 406 (SEM 138) min. Liver survival is anticipated for a cold ischaemic time of up to 12 h using modern preservation fluids (more recently this has been extended to 24 h [9]).

Results of the assays for morphine and its metabolites in plasma are shown in figure 1, and for urine in table III. Plasma concentrations of morphine during the anhepatic period decreased rapidly, consistent with the distribution phase after i.v. injection, followed thereafter by little change. During the anhepatic phase, M3G was detectable in low concentrations in plasma (less than 7 ng ml^{-1}), but urinary concentrations increased to a maximum of 137 ng ml^{-1} . M6G was detected at a maximum of 1.4 ng ml^{-1} in plasma and 22.3 ng ml^{-1} in urine during this phase. Normorphine was undetectable in both plasma and urine throughout both the anhepatic and the

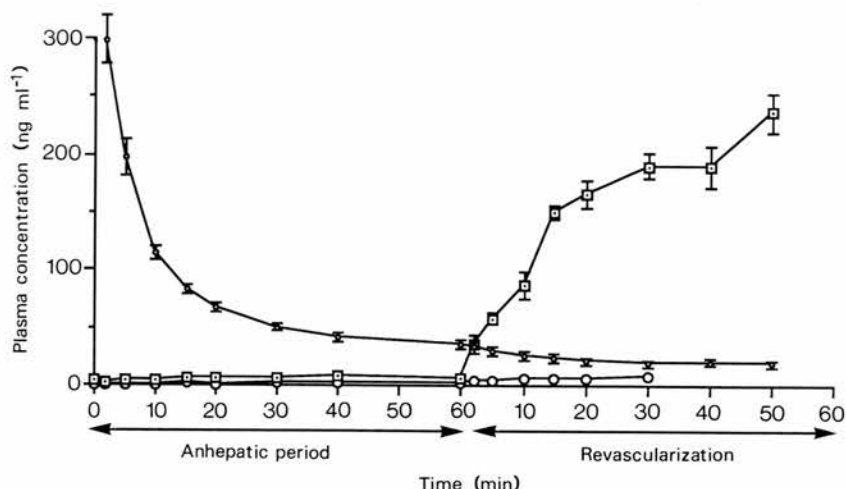


FIG. 1. Mean (SEM) plasma concentrations of morphine (●), M3G (□) and M6G (○) during the anhepatic and reperfusion phases of orthotopic liver transplantation.

TABLE III. Urinary concentrations (mean (SEM)) of morphine, morphine-3-glucuronide and morphine-6-glucuronide during the anhepatic and reperfusion phases of liver transplantation in seven patients

	Morphine (ng ml ⁻¹)	M-3-G (ng ml ⁻¹)	M-6-G (ng ml ⁻¹)
Baseline	0	0	0
Anhepatic phase			
5 min	0	4.1 (2.1)	8.8 (4)
30 min	315 (105)	31 (15)	5.8 (3.2)
60 min	2167 (424)	137 (39)	22 (6)
Reperfusion phase			
30 min	1402 (305)	66 (24)	13 (7)
60 min	812 (307)	132 (44)	11 (6)

reperfusion phases of the study. Mean concentrations of both plasma and urinary M3G increased rapidly on reperfusion of the transplanted liver, to a maximum of 236 ng ml⁻¹ and 132 ng ml⁻¹, respectively. Mean M6G concentrations increased in plasma to a maximum of 7.1 ng ml⁻¹ and decreased slightly in urine, to 11.4 ng ml⁻¹, during this period of the study.

DISCUSSION

The primary site of metabolism of morphine after therapeutic doses has been debated; so also has the clinical importance of the glucuronide metabolites [10–12] which have been shown to be active in animals [13] and man [14]. Clinical and

laboratory studies have suggested two significant sites for morphine metabolism: the liver and kidneys. *In vitro* studies of isolated kidney and liver have shown the presence of uridine diphosphoglucuronyl transferase (UDP glucuronyl transferase) [15, 16], although these do not relate necessarily to function *in vivo* (unpublished observations).

The historical conception of the liver as the major organ of morphine metabolism was contested by the studies in patients with renal failure discussed above and by studies suggesting normal pharmacokinetics in patients with cirrhosis [17]. However, a more recent study in such patients has shown a decrease in the clearance of morphine [18]. The differences between these studies may be related to the severity of the liver disease in the patients studied, but comparisons between patients are difficult, as conventional tests of liver function are poor predictors of changes in pharmacokinetics of drugs [19]. The metabolism of other drugs which undergo glucuronidation suggests that glucuronidation [20] may be relatively spared compared with other metabolic functions, such as oxidation, in severe liver disease. The alternative explanation is that the enzyme system UDP glucuronyl transferase is found in other extrahepatic sites such as the gut or kidney and these may be significant sites for metabolism in man.

Hug and colleagues [21] measured morphine metabolism during the anhepatic phase of liver

transplantation in man, but could not measure the metabolites directly. They found insignificant metabolism during this period. In contrast, studies in the functionally anhepatic dog showed that morphine was glucuronidated in approximately equal degrees by hepatic and extrahepatic tissues [22].

The lack of significant metabolism of morphine in our patients during the anhepatic period of liver transplantation suggests that, in the group of patients studied, the liver is the predominant organ of morphine metabolism. It is clear also that the transplanted liver begins to metabolize morphine rapidly, shortly after reperfusion. A previous study in this centre, using an identical technique measuring the metabolism of midazolam, demonstrated the presence of both major metabolites of midazolam (alpha-hydroxy midazolam and 4-hydroxy midazolam) during the anhepatic period [23]. The difference between the metabolism of midazolam and of morphine during the anhepatic period may be explained by the different metabolic pathways: midazolam undergoes phase I metabolism to its metabolites, whilst morphine metabolism is principally phase II. It is possible, therefore, that phase II metabolism is limited primarily to the liver.

Blood loss and subsequent replacement during the study would have a small dilution effect on measured morphine and metabolite concentrations. However, the loss was continuous rather than sudden in the patients studied. Bolus i.v. administration of drugs results in a rapid increase in plasma concentration and (with morphine) rapid distribution outside the vascular compartment. During this time the amount of blood lost and transfused was small. Similarly, during the elimination period studied, the contribution of blood loss and replacement, even of this magnitude, was small. Thus small changes in plasma concentrations of morphine and its metabolites resulting from blood losses and replacement may have occurred, but significant changes in pharmacokinetic parameters are unlikely.

The lung is known to metabolize and take up selectively certain endogenous and exogenous substances [24]. Studies in anaesthetized and postoperative patients showed significant uptake, but no metabolism of morphine [25, 26]. Although not metabolically active, the lung is thought to act as a reservoir for morphine and other basic drugs.

Increased clinical effects after morphine ther-

apy in patients with renal failure suggested that the kidney may be important in morphine metabolism [2, 3]. This appeared to be supported by pharmacokinetic studies using non-specific assays which did not differentiate between unchanged morphine and its metabolites [1]. More recent work using HPLC [27] and a specific radioimmunoassay [28] has shown increased volumes of distribution and cumulation of metabolites, but no decrease in clearance of unchanged morphine in patients with end-stage renal disease. Thus it is thought that the cumulation of these metabolites (which are pharmacologically active) is the cause for the apparent sensitivity to morphine in patients with renal failure.

The appearance of morphine metabolites in urine during the anhepatic period, despite the plasma concentrations being undetectable, may be explained in two ways. The kidney may be concentrating the small quantities of morphine metabolites in the plasma which are undetectable by HPLC. Alternatively, the kidney could be an extrahepatic site for morphine metabolism (although, if it were, significantly larger concentrations of metabolites would be expected in urine).

Within the constraints of this model, we conclude that the liver is the major site of morphine metabolism in man.

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PHARMACOKINETICS OF MORPHINE IN PATIENTS FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

M. P. SHELLY, K. G. QUINN AND G. R. PARK

Little information is available on the disposition of morphine in patients following liver surgery. There have been several reports of morphine pharmacokinetics in normal volunteers and surgical patients [1-3], but confusion remains on its disposition because of differences between the design of studies and analytical specificity for morphine [4-6]. Investigations have shown both normal [7] and abnormal [8] clearance of morphine in cirrhosis. It was proposed that these differences were related to the severity of hepatic dysfunction in the two groups studied. In addition, morphine clearance has been found to be decreased in septic shock [9].

Classically, the liver has been considered the major site of metabolism, principally glucuronidation, but a renal metabolic role has been postulated more recently [10-12]. We studied the pharmacokinetics of morphine, particularly to see how, in the period immediately following orthotopic liver transplantation, patients metabolize and excrete morphine. At this time, the newly transplanted liver has been subjected to two operations (donor hepatectomy and recipient operation). Additionally, there are periods of warm and cold ischaemia during the operations and transport of the donor liver which may further impair hepatic function. We believed, therefore, that study of these patients may provide information that would be difficult to obtain from other more heterogeneous groups of patients. This group of patients is of further interest because it is possible to collect simultaneously blood, urine and bile.

SUMMARY

Plasma and urine concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide were measured in seven patients after orthotopic liver transplantation. After a single i.v. bolus of morphine sulphate 10 mg a biexponential decay was observed. Although the distribution and elimination half-lives for morphine were similar to those described in previous studies, a greater total apparent volume of distribution was observed. This was reflected in a greater plasma clearance of morphine than has been reported previously. The concentration of morphine glucuronides remained increased 24 h after administration of morphine; the clinical significance of this remains to be established. The metabolism of morphine was virtually complete, with 4.5% unchanged morphine recovered in urine 24 h after drug administration.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained from seven subjects (five female, two male; ages 19-52 yr (mean 36 yr); weights 37-96 kg (mean 64 kg) (table I)) before operation. Both the anaesthetic technique and the surgical procedure have been described previously [13-15]. The perioperative use of morphine and its derivatives was avoided and fentanyl used to provide analgesia. After operation, patients were transferred to the Intensive Care Unit and, when haemodynamic stability had been achieved, a baseline 10-ml blood sample was taken from a radial arterial cannula placed for perioperative monitoring. Samples of urine and bile were obtained also. Morphine sulphate 10 mg was diluted to 10 ml with 0.9% saline and injected over a 2-min period through a centrally placed venous catheter.

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TABLE I. *Details of patients studied*

Patient No.	Sex (M/F)	Age (yr)	Weight (kg)	Diagnosis
1	F	52	96.0	Hepatoma
2	M	36	71.8	Budd-Chiari syndrome
3	M	35	41.0	Hepatoma
4	F	19	82.0	Budd-Chiari syndrome
5	F	37	55.0	Wilson's disease
6	F	26	50.8	Hepatocellular carcinoma
7	F	44	37.0	Primary biliary cirrhosis

This dose of morphine was chosen after previous studies with morphine 2.5 mg i.v. [16] and 5 mg i.v. (unpublished observation) had demonstrated the safety of the larger dose in this group of patients. Blood was sampled further at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 12, 18 and 24 h after drug administration. Urine and bile specimens were collected at 1, 2, 3, 4, 5, 6, 12, 18 and 24 h after drug administration.

Blood samples were placed in a tube containing lithium-heparin anticoagulant and mixed. The tubes were centrifuged at 3000 *g* and the supernatant plasma removed and stored in siliconized tubes at -20°C before analysis. During the study period, the patient was managed as described previously [17] and additional analgesia was provided with bolus doses of fentanyl, which does not cross-react with the assay method. Laboratory investigations (including liver function tests and creatinine clearance) were measured during the 24 h of the study period. In addition, during surgery following revascularization of the liver, hepatic arterial blood flow was measured using a Statham SP12 electromagnetic flowmeter.

Morphine analysis

In order to obtain the required degree of sensitivity and specificity, plasma and urine morphine were measured by a radioimmunoassay procedure validated previously. This utilized an extraction procedure to exclude metabolites from the measurement [18]. Plasma and urine morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) concentrations were measured by a modification of a previously described high pressure liquid chromatography (HPLC) technique [19]. The reference standards used were morphine sulphate pentahydrate (Napp Research Centre Ltd, Cambridge) and M3G (Sigma Chemical Corporation Ltd, Poole, Dorset); M6G was synthesized using a modification of an earlier technique [20]. Samples were pre-

pared in control plasma or urine for calibration, quality control and validation. Calibration curves were constructed for all compounds.

Before HPLC, morphine metabolites were extracted from plasma and urine using solid phase Bond Elut C18 cartridges (Jones Chromatography, Llanbradach, Glamorgan). Subsequent quantification was by HPLC using fluorescence detection at 349 nm to estimate M3G concentrations and coulometric detection at $+0.9\text{ V}$ (*v.* silver-silver chloride) to measure M6G concentrations. The lower limit of detection for M3G was 10 ng ml^{-1} and for M6G by electrochemical detection was $1\text{--}2\text{ ng ml}^{-1}$.

Pharmacokinetic analysis

Plasma morphine data was fitted to a two-compartment model by the method of non-linear least squares analysis [21]. The curve-fitting procedure gave calculations for the area under the plasma concentration *v.* time profile (AUC), distribution half-life ($T_{1/2}^{\alpha}$), the elimination half-life ($T_{1/2}^{\beta}$), the volume of the central compartment (V_1), the apparent volume of distribution (V_d^{area}) and the total clearance (Cl).

RESULTS

Postoperative liver function tests, creatinine clearance, ischaemic time and intraoperative hepatic arterial blood flow for each patient are shown in table II. No patient had major renal impairment during the period of study; in all cases creatinine clearance exceeded 50 ml min^{-1} [22].

Following injection of morphine, an exponential decline in plasma concentration was observed, with no morphine detectable after 24 h (fig. 1). Four hours after administration of morphine (peak concentration for M3G), concentrations of M3G exceeded the parent drug nearly 10-fold. The results of the pharmacokinetic analysis are summarized in table III.

TABLE II. Postoperative liver function tests, plasma creatinine and hepatic ischaemic times in seven patients. GPT = Plasma glutamic pyruvic transaminase; AP = plasma alkaline phosphatase; HABF = hepatic arterial blood flow; NR = normal range

Patient No.	Bilirubin ($\mu\text{mol litre}^{-1}$)	GPT (u. litre $^{-1}$)	AP (u. litre $^{-1}$)	Creatinine clearance (ml min $^{-1}$)	Ischaemic time (min)		Intraoperative HABF (ml min $^{-1}$)
					Warm	Cold	
1	76	84	223	54.8	391	130	420
2	328	136	387	101	267	47	140
3	228	2120	385	63.3	284	71	60
4	37	412	181	88	259	42	400
5	40	181	301	63.7	254	59	1000
6	47	148	258	54.3	231	34	213
7	79	104	484	54.6	236	31	600
NR	2-17	7-40	30-135	90-120			

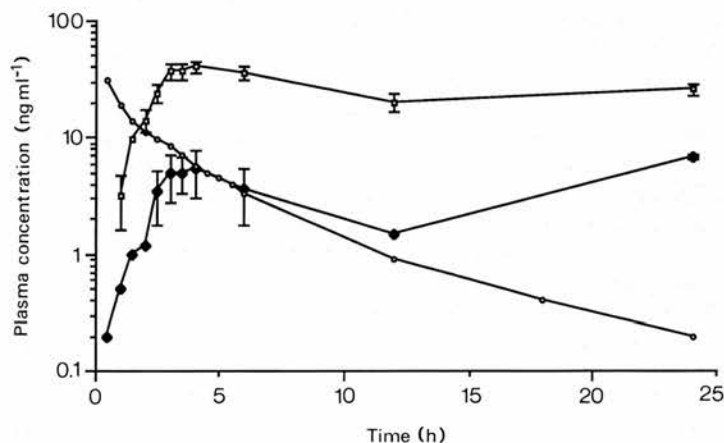


FIG. 1. Plasma concentrations of morphine (○), M3G (□) and M6G (◆) following i.v. administration of morphine sulphate 10 mg in patients following liver transplantation.

TABLE III. Pharmacokinetic parameters calculated after morphine sulphate 10 mg i.v. in patients following orthotopic liver transplantation. $T_{1/2}^{\alpha}$ and $T_{1/2}^{\beta}$ = distribution and elimination half-lives; V_1 = volume of the central compartment; V_d = apparent volume of distribution; Cl = total body clearance of morphine, normalized for body weight; AUC = total area under the plasma morphine concentration v. time curve (0- ∞)

Patient No.	Body weight (kg)	Age (yr)	$T_{1/2}^{\alpha}$ (min)	$T_{1/2}^{\beta}$ (min)	V_1 (litre kg $^{-1}$)	V_d (litre kg $^{-1}$)	Cl (litre kg $^{-1}$)	AUC (ng h litre $^{-1}$)
1	96	52	28.5	252	1.53	3.78	0.62	125.8
2	71.8	36	31.3	198	1.94	4.8	1.09	103.9
3	41	35	15.0	130	3.26	10.7	3.44	53.4
4	82	19	27.4	231	1.49	3.9	0.70	130.3
5	55	37	43.3	320	3.27	14.3	1.86	73.7
6	50.8	26	15.5	212	1.26	7.0	1.38	107.5
7	37	44	20.1	175	2.51	10.3	2.46	82.7
Mean	61.9	36	26	217	2.2	7.8	1.65	96.8
SEM	8.3	4	4	23	0.3	1.5	0.4	10.6

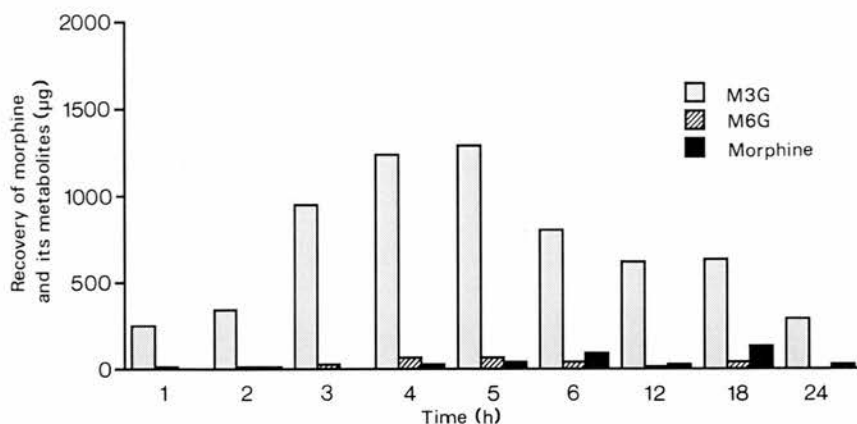


FIG. 2. Mean urine recovery of morphine, M3G and M6G following i.v. administration of morphine sulphate 10 mg in patients following liver transplantation.

Elimination of M3G, like M6G, appeared to be slow, with detectable concentrations of both metabolites at 24 h. Because of this it was not possible to derive any pharmacokinetic parameters for the elimination of the glucuronides, since no further plasma samples were taken after 24 h. Intraoperative hepatic arterial blood flow, which was very variable, did not appear to relate to the postoperative clearance. Recovery of morphine at the 1 ng ml^{-1} level (limit of detection) was 89%. Recovery from plasma and urine for both glucuronides was greater than 90%.

Morphine was recovered predominantly as M3G (85%), with 3.6% as M6G and only 4.5% as the unchanged drug (fig. 2). The remainder of the morphine dose may be either accounted for in the systemic circulation (fig. 1) or excreted in the bile. An attempt was made to analyse morphine, M3G and M6G in bile specimens, but this was not reliable, because of co-eluting compounds.

DISCUSSION

This study determined the pharmacokinetics of morphine following the i.v. administration of morphine sulphate 10 mg to seven patients following liver transplantation. The analytical method combined solid phase extraction and radioimmunoassay to measure unchanged morphine in plasma and urine, whilst excluding morphine glucuronides [18]. In addition, the glucuronides were analysed by a modification of an HPLC technique to quantify M3G by fluorimetric detection and M6G by coulometric detection [19].

A bi-exponential decrease in plasma morphine

concentration was evident in each patient. A more rapid distribution phase has been observed in other studies, but the first sampling point in our study was 30 min after drug administration and this phase was, therefore, not seen. The elimination half-life was 2.4 h; earlier studies using specific assays for morphine have found similar elimination half-lives of approximately 2 h [3, 5, 6].

The plasma clearance of morphine in this study ($1.65 \text{ (SD } 0.4) \text{ ml min}^{-1} \text{ kg}^{-1}$) was greater than previous estimates in healthy volunteers and surgical patients [23] and the recovery of morphine and morphine glucuronides from urine indicates that the excretion of morphine was virtually complete. In addition, the wide range of clearances found may be a reflection of the interpatient variability in chronically ill subjects with pre-existing liver disease. Clearance values greater than hepatic arterial blood flow were observed in four of the seven patients. However, the contribution of portal blood flow to the clearance was not assessed and probably explains this discrepancy. Alternatively, some extrahepatic sites of morphine metabolism may exist.

Patients with impaired renal function show prolonged opioid action following morphine [10]. This has been attributed recently to cumulation of M6G which is pharmacologically active [1, 24, 25]. Patients with chronic liver disease may have impaired renal function, although perioperative renal protection with low dose dopamine may be beneficial [26]. In addition, the periods of stress, surgical trauma and drug therapy may induce a period of oliguria when renal elimination of drug metabolites is impaired [27]. The patients in this study had adequate renal function during the

period of investigation, as indicated by a creatinine clearance in excess of 50 ml min⁻¹.

Although the elimination half-life would appear to coincide with documented values, the estimates for volume of distribution and clearance differ. The disposition of morphine in patients with liver disease has received limited study. The combination of age, disease, anaesthesia and surgery may have contributed to the observed values found for volume of distribution and clearance and may explain the discrepancy with other pharmacokinetic studies.

In this group of patients the metabolism of morphine was found to be almost complete, with only 4.5% of unchanged morphine recovered in urine after 24 h. Total clearance was found to be greater than liver blood flow, indicating the possibility of extrahepatic metabolism. Further use of these specific methods for morphine assay may allow the exact sites of non-hepatic metabolism to be determined.

ACKNOWLEDGEMENT

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Without being informed that the NHS management board had invited district general managers to "express an interest," our health authority, on 20 April 1989, debated how it might react if an instruction was given in future that it would have to choose some form of self governing status. Various options were discussed and it was agreed that if in future we were unable to remain with the status quo perhaps the best option for patient care would be for the whole district of North Devon to become a self governing trust. No formal vote was taken and the matter appeared to be hypothetical, with the assumption that there would still be much to be debated and discussed in the future.

You can therefore imagine the consternation among the medical members of the health authority when they were informed by the district general manager on 10 May 1989—the day before the *Independent* was due to publish the list of districts "expressing an interest"—that he had written a letter to the regional general manager on 3 May formally to "express an interest in forming a self governing trust for the whole district" and indicating that this application had the full support of all the medical members of the health authority.

It would be interesting to find out how many other doctors in other districts have been similarly misrepresented into becoming Mr Clarke's "willing volunteers."

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1 Warden J. Clarke steps out. *Br Med J* 1989;298:1478. (3 June.)

SIR,—Bassetlaw has recently been quoted in the House of Commons¹ and in the press as "expressing an interest in becoming self governing" and we are aware that pressure has been brought to bear on other districts to follow, using our own as an example. Clinicians and other staff, when consulted, have supported this on the basis that the hospital and community services would be a part of one composite unit. However, we are not prepared to support the furtherance of this idea without considerably more information.

We all believe that evaluation of the resource management initiative and application of the lessons learnt from it would be far more likely to improve patient care than would the introduction of self governing trusts and general practice budgets in the way described in the white paper. However, we have not objected to the "expression of interest" by our district for specific local reasons.

Our district was established in 1982 because of considerable local opposition to its incorporation into nearby districts. It was at the time one of the, if not the, most underfunded district in Britain and facilities for medical care were appalling. This situation has improved with the opening of the first phase of the district general hospital, and community and priority services have improved dramatically despite continued underfunding. This has occurred with persistent lobbying of those directly responsible for funding, and we are convinced that the dissolution of the district, as would happen with the implementation of the white paper proposals, would undermine our ability to provide appropriate care for our patients.

We fear that separating the district general hospital services from community services would introduce a damaging element of competition between unlike services. A situation could easily develop where patients would be discharged early to community services, which could disclaim or only grudgingly accept responsibility for their care, leading to the sort of divide between authority managed services and trusts which at present bedevils community care of the mentally ill and for which the second Griffiths report was commissioned.

Our dilemma is that of protecting specific local

needs while supporting professional recommendations. The government's intention to introduce competition into the service by separating those responsible for providing the service from those operating it can probably be achieved by using lessons from the resource management initiatives. If the principle can be established that such operators must provide both hospital and complementary community services the danger of gaps arising in services would be reduced. If agreement on the maintenance of nationally determined, although inevitably more flexible, standards, pay, and conditions of service can be reached perhaps we can preserve a National Health Service. Bassetlaw most certainly does not wish to "opt out" of it.

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1 Owen D. Opposition day motion. *House of Commons Official Report (Hansard)*. 1989 April 18;151:cols 201-43 (No 87.)

Isoflurane compared with midazolam in the intensive care unit

SIR,—We are concerned about certain features of the study of sedation of the critically ill reported by Dr K L Kong and others.¹ They quote Geller *et al* as reporting dangerous complications from the use of flumazenil, but in this paper no untoward haemodynamic or respiratory effects were reported.² In one patient it was necessary to infuse flumazenil for five hours, but this cannot be considered dangerous in an intensive care unit. We have infused flumazenil for prolonged periods³ without hazard, although it is expensive.⁴ Dr Kong and others also correctly quote the rapid rise in intracranial pressure associated with the reversal of midazolam⁵ as dangerous to the patient, but such vulnerable patients are surely a group in whom isoflurane sedation would also be inapplicable and would have been excluded from the study.

The authors also state that the effective dose of isoflurane in their study was confined to a narrow range (0.1-0.4% concentration), whereas the requirement for midazolam showed considerable variability among patients (0.014-0.140 mg/kg/hour). The dose of isoflurane will depend on many factors including the minute volume, alveolar ventilation, and cardiac output. There was no variation in the concentration of midazolam used (0.1%). The way in which the authors discussed dose equivalents is misleading.

We wish briefly to report on two patients in whom other sedatives (midazolam, propofol, ketamine, and narcotics) proved ineffective and isoflurane was useful but presented other problems. The first patient was a 21 year old girl who required sedation after combined liver and kidney transplantation that was complicated by acute tubular necrosis (managed with continuous haemofiltration and dialysis), recurrent sepsis, and life threatening gastrointestinal haemorrhage. She remained agitated and distressed while receiving a midazolam infusion at up to 15 mg/hour and bolus doses of morphine. Effective sedation was finally achieved with a combination of 0.5-2.0% isoflurane and continuous intravenous infusion of midazolam (10 mg/hour) and subsequently of alfentanil (8 mg/hour). Because of concern about nephrotoxicity from fluoride released from the breakdown of isoflurane and her potential failure to eliminate it the serum fluoride concentration was measured after six days of treatment and found to be 18 µmol/l (normal range 5.3-10.5 µmol/l). Although this is

not at the toxic level (50 µmol/l), it is greater than that previously reported with isoflurane.⁶ Will even higher concentrations be achieved in critically ill patients who receive isoflurane for longer periods or in whom an efficient method of renal replacement treatment is not used?

The second patient was a 15 year old boy who required ventilatory support for a severe asthma attack. He received 0.25-1.0% isoflurane in addition to fentanyl and midazolam or propofol by infusion.

Although it was a useful technique, ducting of the expired gases away from the ventilator was a problem. Dr Kong and others do not tell us explicitly how this was achieved. When we used it one of the limiting factors was having the patient next to a window; perhaps activated charcoal may be one answer to this problem. Cost must also be considered. The ventilators used in Dr Kong and others' study and for our patients were open circuit ventilators needing large flows of fresh gas. The estimated cost of isoflurane for our first patient was £1200 over the six days (midazolam 10 mg/hour cost £19.20 per 24 hours and alfentanil 8 mg/hour cost £107 per 24 hours), and for the second patient the total cost of isoflurane for three days was £1500. We used higher concentrations than Dr Kong and others described, and their method will result in some savings in cost.

Isoflurane will probably be a valuable addition to our therapeutic options for sedation of the critically ill, but it will require further evaluation over longer periods of time before it is introduced into routine clinical practice.

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Acute mountain sickness

SIR,—It is disappointing that an essay by a doctor should advocate drug treatment without once mentioning simpler, much more effective measures. Dr S B Blunt suggests that acetazolamide should be indicated for the prophylaxis of acute mountain sickness; nowhere, however, does she mention acclimatisation.¹

Acclimatisation (slow ascent) is the best prophylactic, and descent is the best treatment. Ignoring these basic facts (with or without drugs) is a main cause of illness and death on mountains. Dr Blunt's own rate of ascent on Kilimanjaro far exceeds that recommended by any standard text or mountain safety authority.

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1 Blunt SB. Acute mountain sickness on Mount Kilimanjaro. *Br Med J* 1989;298:1324. (13 May.)

Anaesthesia and the law

Monitoring

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Arguably, many deaths and injuries from hypoxia could be avoided if more comprehensive monitoring equipment and stricter standards of care were imposed on anaesthetists. Those health authorities and private hospitals and clinics who plead lack of cash as justification for operating with outmoded and inadequate equipment and a shortage of trained staff should think again. Leaving aside the human tragedy of an anaesthetic injury or death, one large legal claim for damages can cost more money than ever could be saved by shortsighted economies. Having said that, it is clear that limited cash resources must make for difficult choices; the provision of a new ECG monitor or pulse oximeter, for example, may deprive other departments of valuable equipment and staff or reduce the number of treatments given and so forth.

In Massachusetts, USA, stricter practice standards for anaesthetists are paying off financially. Since these have been in force claims have dramatically reduced and lower premiums are the order of the day, with more reductions planned if the trend continues. Anaesthesia will become a low risk specialty for insurers.¹ In New York State, regulations are being proposed that will require specific monitoring devices to be used during anaesthesia. Further, and in response to the Libby Zion case,² there are hopes that maximum hours of work per week will be imposed on junior hospital doctors in New York State in the hope of reducing medical misadventures occurring as a result of fatigue. Though there is much concern about fatigue and long hours in Britain, attempts to legislate in Britain seem doomed to fail.

Similarly, recommendations for stricter standards in anaesthesia remain counsels of perfection with no mandatory force as, for example, suggestions that ECG monitoring should be performed during all routine anaesthesia.³ The Association of Anaesthetists of Great Britain and Ireland has published recommended standards of monitoring (1988); but, again, these standards do not have the force of law and are not uniformly complied with across the country.

Following an anaesthetic disaster can the plaintiff or his family claim that a failure to follow such recommendations was negligent and caused the injury? In my view, though such guidelines would be persuasive, noncompliance (often through lack of resources) would not necessarily render the anaesthetist or his hospital negligent and it would depend on all the circumstances. The law requires a doctor to be reasonably competent and to provide a reasonable standard of care which may not be optimum. Thus, if the doctor can satisfy the court that he (or she) has complied with a practice considered proper by a responsible body of medical opinion in his field and that he provided a reasonable standard of care to the patient he will not be found negligent.⁴

However, on 9 November 1988, following a Fatal Accident Inquiry into a death arising from dental anaesthesia, a

Scottish Sheriff recommended that 'urgent anxious and careful consideration be given by the Authorities to the adoption' of ECG monitoring and the attendance of a state registered nurse trained in resuscitation techniques 'in every case where a general anaesthetic is administered in a dental clinic or a dental surgery'.

In that case an 11-year-old girl was given nitrous oxide, oxygen and halothane by a trained anaesthetist to allow for extraction of four teeth. A standard inhalation technique was used. After the third tooth had been extracted the halothane was stopped and after removal of the fourth tooth the mask was taken off. The child was still breathing easily but then her breathing became shallow and intermittent. The anaesthetist tipped her chair back, gave oxygen via a facemask and rubbed her sternum. This caused an intake of breath but no movement. Her pulse became weaker and he tilted the chair so that her head was below her feet; she was breathing shallowly. She was placed on the floor, breathing intermittently from the oxygen mask but with no pulse.

The anaesthetist then requested a defibrillator from the recovery room and an ECG trace confirmed that the child had suffered a cardiac arrest. The trace showed ventricular fibrillation. He then inserted a Brook airway and the dentist performed expired air resuscitation. The anaesthetist believed there was sufficient oxygenation of the patient to permit defibrillation but he was unable to restore the heart rhythm, and after the first application asystole occurred. Cardiac massage and lignocaine produced a very slow heart trace three times but breathing could not be maintained and the patient died 2 days later in hospital.

The sheriff determined that the child's death might have been avoided if an electrocardiograph had been used to monitor her heart, a state registered nurse trained in resuscitation techniques had been in attendance, and if the patient's trachea had been intubated and her lungs ventilated using a tracheal tube with 100% oxygen immediately cardiac arrest had been diagnosed. (At the inquiry, the anaesthetist was criticised by the sheriff's medical expert for failing to intubate promptly and that this should have been his first priority rather than defibrillation.)

The sheriff said that 'the most significant evidence in the inquiry was the ready acceptance that acute cardiac failure can occur during dental anaesthesia even when an impeccable anaesthetic technique is employed by an experienced anaesthetist. Anyone who has teeth extracted under general anaesthetic is at risk. In these circumstances a requirement to resuscitate a patient is to be anticipated. Adequate personnel and equipment should be on hand to maximise the possibility of a successful resuscitation.' The anaesthetist had the greatest difficulty in carrying out the resuscitation attempt in the absence of skilled assistance as three procedures were required immediately and he could not carry them out by himself at the same time.

Another significant piece of medical evidence given to

these symptoms may represent rapid awakening of the patient in an apparently hostile environment. The apparent safety of flumazenil does not preclude the need for careful dose titration. Adverse cardiovascular responses similar to those seen after naloxone¹³ may occur if patients are awakened suddenly with a tracheal tube in place, although this has not been reported to date. Cardiovascular instability has not been reported in studies of reversal of sedation after coronary angiography,¹⁴ but these patients had neither a tracheal tube in place nor a painful surgical incision. The short duration of action of flumazenil (about one hour) may necessitate repeated bolus doses or an infusion in cases of significant benzodiazepine accumulation.

The prolonged benzodiazepine sedation in these patients may be explained by drug accumulation due to the delayed elimination that occurs in the elderly,¹⁵ the critically ill (particularly those with sepsis)^{2,3} and a subgroup of the normal population.⁴ This is supported by the observation that several of the patients in this study required very small daily doses of midazolam. Alternatives to the use of midazolam are few. Propofol is being investigated currently for this purpose and may prove useful, although we have noticed some haemodynamic instability with this agent, especially in jaundiced patients (unpublished observation). Volatile agents (particularly isoflurane) are also under investigation and may prove useful in the future if the problems of atmospheric pollution and cost are resolved. The exact place of these alternatives compared to the use of midazolam, combined in some patients with the use of the antagonist, remains to be clarified.

The four patients who required a flumazenil infusion needed less than has been calculated theoretically to be necessary (1.44 mg/hour) by Klotz and Kanto.¹⁶ This may indicate that flumazenil, an imidazobenzodiazepine, may be subjected to similar alterations in elimination to those demonstrated for midazolam.^{2-4,15}

The patients who did not show an improvement of conscious level after flumazenil are thought to have had other causes for their depressed conscious level including electrolyte abnormalities, tissue hypoxia, cerebral oedema, and hepatic or septic encephalopathy. The last is a poorly understood condition.¹⁷ All made a full neurological recovery except for one patient who had a hepatic resection and died of liver failure.

Anecdotal reports have suggested that flumazenil may reverse some features of hepatic encephalopathy, mediated via the GABA system;¹⁸ further studies are in progress to evaluate its value in this condition. Two patients who responded to flumazenil had undergone liver transplantation but none of their laboratory investigations supported the development of liver failure, and the improvement in conscious level is thought to be due to reversal of residual effects of midazolam.

Sudden awakening may occur, and result in sudden discomfort, when flumazenil is used in patients who have a tracheal tube in place. This resulted in airway obstruction when the tube was bitten in one of our patients. We were prepared for this eventuality and the addition of isoflurane to the inspired gas resolved the situation rapidly. Not all ventilators have the facility to add vapours to the inspired gas. It may be prudent to have ready a suitable dose of a short acting intravenous anaesthetic agent, such as thiopentone, when a patient whose trachea is intubated is to receive flumazenil. The short action of flumazenil makes it unlikely to be a problem of prolonged duration.

In conclusion, flumazenil appears to be a useful agent for reversal of unexpectedly prolonged benzodiazepine seda-

tion in critically ill patients. The short duration of action of flumazenil necessitates either a continuous intravenous infusion or repeated bolus doses if significant benzodiazepine accumulation has occurred. Other recoverable causes of depression of conscious level must be considered if flumazenil does not reverse sedation.

Acknowledgments

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Table 1. Sedation score used to assess change in conscious level of critically ill patients after the administration of flumazenil. A significant response was defined as an increase of three points or more.

1. Alert, writing coherent messages
2. Alert, writing meaningless but legible letters
3. Alert, writing unintelligible scrawl
4. Alert, unable to write
5. Awake, but confused
6. Awake, agitated
7. Awakens with soft spoken voice
8. Awakens with loud voice
9. Awakens with gentle shaking
10. Awakens with glabellar tap
11. Responds to fingernail pressure in a purposeful way
12. Responds to fingernail pressure in an unpurposeful way
13. Does not respond to fingernail pressure

administration of flumazenil. The short duration of action of flumazenil led to resedation in seven of these patients within one hour of its administration. One patient required resedation with isoflurane when she bit her tracheal tube and caused partial airway obstruction. Four patients received an infusion of flumazenil to maintain the improvement in conscious level (Table 3). The infusions were required for a period of 8 hours to 10 days and were given at a rate of 0.5–1 mg/hour. The patient who required flumazenil for 10 days has been reported previously.¹¹ The success of flumazenil could not be related in a consistent pattern to age, sex, pathological processes, or APACHE II score due to the wide interpatient variability. In addition, the midazolam dosage, duration of sedation and time after discontinuation of midazolam did not correlate with the effects of flumazenil.

There were no unwanted effects of flumazenil such as nausea and vomiting in any of these patients. Blood pressure and heart rate increased in five patients by 5–20 mmHg and 12–25 beats/minute respectively.

Eleven patients received significant quantities of opioids during the sedation period. These patients received naloxone to evaluate whether opioid-related sedation was present. Two patients (18%) exhibited an improvement in conscious level of two points after naloxone but showed no further improvement with flumazenil.

Five patients did not respond to the administration of flumazenil. One of these had received a liver transplant. The donor organ had been ischaemic for an unusually prolonged period before revascularisation during the donor operation. He was sedated for 48 hours postoperatively. A cranial computerised tomogram was obtained when he did not awaken after flumazenil, and this showed possible cerebral oedema. Consequently, his lungs were ventilated artificially to produce hypocapnia (P_{aCO_2} 3.5–4.5 kPa); neuromuscular blockade was used to prevent coughing and struggling, and opioids to provide sedation. He had awoken when the myoneural blocking agents were reversed 48 hours later. A second patient had also undergone liver retransplantation due to chronic rejection after her first

Table 2. Details of the 13 patients who received flumazenil to reverse the effects of midazolam. Data are presented as mean (SD).

Females/males	8/5
Age, years	49.2 (19.6)
APACHE II	18.6 (5.8)
APACHE II without GCS	10.6 (4.1)
Duration of sedation, days	5.6 (5.2)
Time since last midazolam administration, hours	28 (24)
<i>Presenting diagnosis</i>	
Liver transplant recipient	5
Multiple trauma	3
Colonic surgery	3
Septicaemic shock	2

transplant (for primary biliary cirrhosis). She required small doses of both morphine and midazolam after operation; only 10 mg of each was given in the first 24 hours. She did not respond to either flumazenil or naloxone but awoke spontaneously 12 hours later. One patient who underwent a difficult hemihepatectomy, complicated by a 30-litre blood loss, did not show any improvement in consciousness when either antagonist was administered, and did not make a spontaneous neurological recovery. It was thought that the coma was due to progressive hepatic failure and encephalopathy, and eventually the patient died without regaining consciousness. One patient had suffered massive trauma that necessitated bilateral lower limb amputations and several extensive operations to deal with the degloving injury to her abdomen. A minor head injury was sustained also. She developed acute renal failure as a consequence of these injuries. She had received large amounts of both midazolam and opioids; large, but carefully titrated, doses of flumazenil (5 mg) and naloxone (1.2 mg) had no effect. She regained consciousness spontaneously one week later. One patient required intensive care after a difficult colectomy for diverticular disease. There were extensive adhesions within the abdomen and the operation was complicated by excessive bleeding (15 litres). Her trachea was extubated after 48 hours of ventilatory support, but she became progressively confused with deterioration in her respiratory function. She received flumazenil at this time in an attempt to reverse any residual effects of benzodiazepines (including the confusion) and to try to avoid the need for reinstitution of ventilatory support. There was no response to the flumazenil, and ventilatory support was restarted. She awoke gradually over the next 48 hours.

Discussion

Flumazenil is a specific benzodiazepine receptor antagonist. It has been shown to be a safe agent for the reversal of short-term benzodiazepine sedation in patients who require intensive care.¹² The only adverse effects that have been reported in critically ill patients have been nausea and vomiting. Fear and anxiety have been described if large doses (more than 10 mg) of flumazenil are given rapidly but

Table 3. Details of patients who received an infusion of flumazenil.

Age (years)	Sex	APACHE (–GCS)	Days sedated	Total dose midazolam (mg)	Flumazenil infusion
67	F	14	4.0	50	1 mg/hour for 18 hours
78	M	9	4.0	33	0.5 mg/hour for 18 hours
22	M	11	5.0	800	0.5 mg/hour for 10 days
66	M	10	0.5	20	0.5 mg/hour for 8 hours

Reversal of prolonged sedation using flumazenil in critically ill patients

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Summary

Thirteen critically ill patients received flumazenil after multiple doses, or an infusion, of midazolam was used as part of a sedation regimen to facilitate intensive care. All patients remained excessively sedated after the midazolam was stopped for 6 hours or longer. An improvement in conscious level occurred in eight patients (61%). In four of these eight patients, the duration of action of flumazenil necessitated its continued administration by an infusion to maintain the improvement in conscious level. The dose of flumazenil required each hour was less than estimated previously; this indicates that it may be subjected to similar alterations of elimination as those described for midazolam. Flumazenil appears to be a useful drug for the reversal of prolonged benzodiazepine sedation but repeated bolus doses or an infusion are needed if significant accumulation of benzodiazepines has occurred.

Key words

Intensive care.

Hypnotics; midazolam.

Midazolam, a benzodiazepine with a short duration of action, is used frequently to provide sedation in critically ill patients. The principal metabolite is α -hydroxymidazolam, which is believed also to be active in man.¹ Prolonged sedation after midazolam administration is a recognised problem in the critically ill despite the short duration of action of the drug in healthy patients.^{2,3} In addition, 6-10% of the population have a pharmacogenetic abnormality which results in slow metabolism of midazolam.⁴ Both these factors may result in accumulation when a continuous intravenous infusion is administered, and may result in excessive sedation, difficulty in assessment of neurological function, problems with weaning from artificial ventilation and cardiovascular instability. Furthermore, unnecessarily long periods of sedation increase the duration of admission to the intensive care unit, with inefficient utilisation of that resource.

Benzodiazepine sedation is reversible with the benzodiazepine antagonist flumazenil which has been available commercially for some time in Europe.

We administered flumazenil to 13 critically ill patients who remained undesirably sedated after administration of multiple doses or an infusion of midazolam. The midazolam had been stopped for a variable time period of 6 to 72 hours.

Method

Patients were included in this prospective study when they were known to have received during their treatment period significant doses of midazolam which might have contributed to excessively prolonged sedation. Flumazenil was given after a reasonable time for recovery had passed or when it was desirable to awaken the patient for other reasons (neurological assessment, to enhance coughing ability, or to improve ventilatory effort to aid weaning from artificial ventilation).

Patients with known hypertension or ischaemic heart disease were excluded because of the theoretical risk of acute hypertension or myocardial ischaemia which may follow rapid awakening. If a tracheal tube was in place, an isoflurane vaporizer was connected to the ventilator system, to allow rapid resedation if cardiorespiratory instability developed on re-awakening. Analgesia was provided with intercostal nerve blocks if there was a recent abdominal surgical incision. Blood pressure was measured continuously in all patients by means of an intra-arterial cannula, and heart rate and cardiac rhythm were displayed on an electrocardiogram.

Opioids may cause prolonged sedation in critically ill patients, in particular those with renal failure.⁵⁻⁷ Consequently, patients who were thought to have opioid-related sedation were given naloxone in 0.1-mg increments to a maximum of 0.4 mg for reversal of sedation. If there was no significant improvement with naloxone, flumazenil was given in 0.1-mg increments until satisfactory awakening occurred or a total of 1 mg was given.

The APACHE II score⁸ without the Glasgow coma scale (GCS) component was recorded before the administration of naloxone and flumazenil. The GCS component of the APACHE II score may be an entirely reversible element if it is due to excessive sedation and so may increase the score inappropriately.⁹

Sedation was assessed before and after administration of naloxone and flumazenil using a score modified from that described by Ramsay *et al.*¹⁰ (Table 1). An improvement in conscious level was defined as an increase of more than three points on the scale.

Results

The 13 patients studied were of a heterogeneous nature (Table 2). Eight (61%) of the 13 showed an improvement of more than three points on the sedation scale after the

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The Pharmacokinetics of Alfentanil in Patients Following Liver Transplantation

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ABSTRACT

The pharmacokinetics of alfentanil were investigated in seven patients following liver transplantation. Alfentanil clearance was markedly reduced in two patients and suggests that it should be used with care in these patients since a prolonged effect is possible.

KEYWORDS

Pharmacokinetics, Alfentanil, liver transplantation.

INTRODUCTION

Alfentanil is a potent opioid analgesic with a rapid onset and short duration of action. It is cleared almost completely by hepatic biotransformation and is dependent on both hepatic function and blood flow for its elimination. It has a decreased clearance in patients with cirrhosis (Ferrier C et al, 1985) and in a subset of the normal population (McDonnell TE et al, 1982); its clearance is unchanged in patients with renal failure (Van Peer A et al, 1986). Because the action of alfentanil is terminated by metabolism rather than redistribution, it has been used by continuous intravenous infusion to provide sedation and analgesia to patients receiving intensive care. Some patients, however, have demonstrated a decreased clearance of the drug (Yate PM et al, 1986).

Alfentanil is bound in plasma to alpha 1 glycoprotein, an acute phase protein which increases in concentration following injury. The pharmacokinetics of alfentanil were studied on two occasions in patients following liver transplantation to assess the importance of the various factors influencing its pharmacokinetics and to observe any changes in alfentanil pharmacokinetics as the graft liver regained function following operative trauma.

METHOD

Seven consecutive patients were studied immediately following orthotopic liver transplantation. Informed written consent for the study was obtained from each patient and the study was approved by the District Ethics Committee.

Within 3 hours of return to the Intensive Care Unit, a baseline blood sample was collected and alfentanil, 20 mcg/kg diluted to 10 mls in 0.9% saline, was administered as a bolus over 1 minute through a centrally placed venous cannula. Samples of arterial blood were removed at 2, 5, 10, 20, 30, 60, 90, 120, 180, 360, 480, 600 and 720 minutes. At the end of this period, a further 20 mcg/kg of alfentanil was administered in a similar manner and an identical sampling protocol followed.

Blood was collected into lithium heparin tubes, centrifuged and the supernatant plasma separated and stored at -20°C . Subsequent analysis was performed using a radioimmunoassay technique (Michiels M et al, 1983).

RESULTS

Details of the patients are shown in table 1 and their preoperative and postoperative liver function tests in table 2.

Table 1 : Details of the patients studied following liver transplantation. Figures shown as mean \pm standard error, with range for duration of cold ischaemia.

Age	37.9 \pm 3.21 years	
Weight	61.7 \pm 3.38 kg	
Sex	3 male/4 female	
Cold ischaemic period	210 - 389 min	
Anhepatic duration	59.4 \pm 8.61 min	
Diagnosis	Sclerosing cholangitis	3
	Chronic Active Hepatitis	3
	Polycystic liver	1

Alpha 1 glycoprotein levels were normal in all patients throughout the study period. There was considerable variation in the plasma concentrations of alfentanil between the patients and this is quantified in table 3 which shows the pharmacokinetic parameters for the individual patients during both study periods.

Table 2 : Liver function tests (a) before and (b) immediately after liver transplantation.
* = no result available.

Patient	Albumin (g/l)	Total Bilirubin (μ mol/l)	Alkaline Phosphatase (U/l)	Alanine Transferase (U/l)
1 a	29	268	2810	444
b	29	*	*	*
2 a	27	284	115	25
b	29	103	32	84
3 a	14	332	228	86
b	29	226	111	1144
4 a	37	336	163	60
b	32	154	207	233
5 a	26	155	752	67
b	30	41	36	536
6 a	10	195	493	50
b	32	140	364	922
7 a	32	22	904	14
b	31	27	53	57
Normal Range	30 - 44	2 - 17	30 - 135	7 - 40

Table 3 : Elimination half life, clearance and volume of distribution of alfentanil in patients following liver transplantation. 1 = first study period, 11 = second study period.

Patient	T _{1/2} (min)		Clearance (ml/min/kg)		Vd (ml/kg)	
	1	II	1	II	1	II
1	730	330	0.425	0.956	447	455
2	158	66	6.220	3.620	1413	345
3	120	217	8.710	2.210	1502	689
4	82	67	6.630	5.070	780	492
5	267	231	4.110	3.840	1581	1279
6	365	385	0.833	0.807	438	448
7	257	347	3.470	1.930	1284	965
Normal Values	90		6.4		860	

DISCUSSION

Alfentanil elimination is dependent upon hepatic clearance and alfentanil clearance is decreased in patients with cirrhosis. In this study, all the patients had abnormal liver function tests but their alfentanil clearance varied considerably. Only one patient had an essentially normal pharmacokinetic pattern of alfentanil throughout the study period. Four patients had an increased volume of distribution during the first study which decreased during the second study period. In addition all these patients had a low alfentanil clearance during the second study period. Two patients demonstrated considerably prolonged clearance of alfentanil.

These pharmacokinetic alterations suggest changes either in hepatic function or, more likely, changes in hepatic blood flow during the period of observation. However, these changes appear to be unpredictable and may result in unwanted narcosis and respiratory depression.

CONCLUSION

Alfentanil clearance was considerably reduced in two of the seven patients studied following liver transplantation.

Alfentanil should be used with care in patients following liver transplantation since a prolonged effect is possible.

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Extra-hepatic metabolism of midazolam

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Six patients received 10 mg of midazolam intravenously during the anhepatic period of liver transplantation. Arterial blood was sampled during this time and for a similar period following revascularisation. The plasma was analysed using gas chromatography and electron capture detection (GC-ECD) for midazolam α -hydroxymidazolam and α -hydroxymidazolam glucuronide. Five of the six patients had small but significant concentrations of metabolites detected during the anhepatic period, demonstrating the presence of extra-hepatic sites of metabolism for this drug. The remaining patient had plasma concentrations of metabolites below the lower limit of detection ($2\mu\text{g l}^{-1}$). This may represent a pharmacogenetic abnormality or a temporary failure of midazolam metabolism secondary to the patients illness affecting the extra-hepatic sites of metabolism.

Keywords midazolam extra-hepatic metabolism

Introduction

Midazolam is a short acting benzodiazepine and is commonly used to sedate patients requiring brief procedures, to induce anaesthesia and for prolonged sedation during intensive care. It is hydroxylated by the cytochrome P450 system predominately to α -hydroxymidazolam, which has some pharmacological activity, and to a smaller extent to 4-hydroxymidazolam, which is thought to be inactive. Following this, glucuronidation occurs making the compound more water-soluble and allowing renal elimination. In the postoperative period prolonged sedation has been observed (Byatt *et al.*, 1984; Byrne *et al.*, 1984). A reversible failure of metabolism has been demonstrated in patients with sepsis (Shelly *et al.*, 1987) and in a child with acute derangement of liver function following cardiac surgery (Lloyd-Thomas & Booker, 1986). These observations prompted a study on the pharmacokinetics of midazolam in patients following orthotopic liver transplantation (when liver function is deranged due to cold injury, ischaemia and the effects of surgery and anaesthesia following the donor operation and the liver transplant procedure). This study demonstrated normal pharmacokinetic parameters for the parent

drug but the plasma concentrations of the α -hydroxy product were surprisingly high (Shelly *et al.*, 1989).

When orthotopic liver transplantation is performed there is a period of no liver function. This enables the importance of the liver in the metabolism of a drug to be investigated. Several phases in the surgical procedure can be identified. Firstly, the diseased liver is dissected leaving it with its vascular connections intact (skeletonisation). This is followed by clamping of all of the hepatic vessels and removal of the diseased liver, after which the suprahepatic inferior vena cava of the donor liver is anastomosed to the recipient's vena cava and the portal vein or the infra hepatic cava of the donor liver anastomosed to the recipient's vessel (anhepatic period). When these anastomoses are complete the vascular clamps are released (revascularisation). The remaining anastomoses are completed (hepatic artery, portal vein or inferior vena cava), the biliary conduit is fashioned and the abdomen is closed (Calne, 1987). The anhepatic period provides a unique opportunity to study the metabolism of drugs in man. Studies during this period have not been performed previously because of the many

difficulties that may occur at this time (Carmichael *et al.*, 1985); it is only with the increasing experience of this centre that such studies have now become possible without detriment to the patient's well-being.

Method

The study was approved by the Hospital Ethics Committee and written consent was obtained from the six adult patients. The anaesthetic technique was similar to that described previously (Lindop & Farman, 1987) except that benzodiazepine premedication was specifically avoided and a narcotic and antisialagogue was substituted.

Immediately before vascular isolation and removal of the diseased liver a baseline blood sample was taken from a previously sited radial arterial line. As soon as haemodynamic stability was achieved after vascular isolation and removal of the diseased liver (approximately 2 min), 10 mg of midazolam hydrochloride was injected into a central vein and flushed with 10 ml 0.9% sodium chloride. Blood was removed at 2, 5, 10, 15, 20, 30, 40 min or at the end of the anhepatic period and immediately before revascularisation of the new liver. Following revascularisation the sampling protocol was repeated. After removal, blood was placed into tubes containing oxalate anticoagulant, mixed and centrifuged at 3,000 rev min⁻¹. The supernatant plasma was then separated and frozen at -20°C until subsequent analysis by gas chromatography with electron capture (GC/ECD) (Heizman & Von Alten, 1981) for midazolam, α -hydroxymidazolam and α -hydroxymidazolam glucuronide. The lower limits of detection of midazolam and its metabolites were: midazolam

(3 $\mu\text{g l}^{-1}$) α -hydroxymidazolam (2 $\mu\text{g l}^{-1}$) and α -hydroxy-midazolam glucuronide (2 $\mu\text{g l}^{-1}$).

Results

Patient information, details of the anhepatic phase and preoperative liver function tests are shown in Table 1. Liver function had been deteriorating for many years in patients 2, 3, 4 and 5, whereas patient 1 had a 1 month history of deteriorating liver function following administration of an antidepressant, and liver function was normal in patient 6.

The plasma concentrations of midazolam, α -hydroxymidazolam and α -hydroxymidazolam glucuronide in patients 2, 3, 4, 5 and 6 during the anhepatic period and following reperfusion are shown in Figure 1. Metabolites of midazolam were detected in the plasma during the first 15 min of the anhepatic period at low but significant concentrations. Patient 1 did not at any time have detectable plasma concentrations of α -hydroxymidazolam.

Discussion

Five of the six patients clearly demonstrated metabolism of midazolam during the anhepatic period of liver transplantation. Thus, significant concentrations of both α -hydroxymidazolam and α -hydroxymidazolam glucuronide were detected, confirming the presence of extrahepatic sites of midazolam metabolism. The possible sites include the gut (which has been shown to metabolise flurazepam in man (Mahon *et al.*, 1977)), the kidney (which has been implicated in the metabolism of morphine (Moore *et al.*, 1986)),

Table 1 Patient information, details of the anhepatic period and preoperative liver function tests (normal values shown in brackets)

	Patient					
	1	2	3	4	5	6
Sex	F	F	F	F	F	M
Age (years)	34	46	53	54	30	48
Weight (kg)	65	61	52	48	60	74
Diagnosis	SAHN	PBC	PBC	PBC	SC	HEP
Anhepatic period (min)	32	42	43	50	52	86
Blood loss (ml)	200	970	180	130	768	174
Bilirubin ($\mu\text{mol l}^{-1}$) (3-17)	868	428	112	134	309	12
Alanine aminotransferase (U l ⁻¹) (7-40)	1124	188	138	111	99	32
Alkaline phosphatase (U l ⁻¹) (30-135)	167	1022	780	1968	344	127
Prothrombin ratio (1-1.3)	9.9	1.2	1.2	1.2	1.1	1.0

SAHN = subacute hepatic necrosis, PBC = primary biliary cirrhosis, SC = sclerosing cholangitis, HEP = hepatoma.

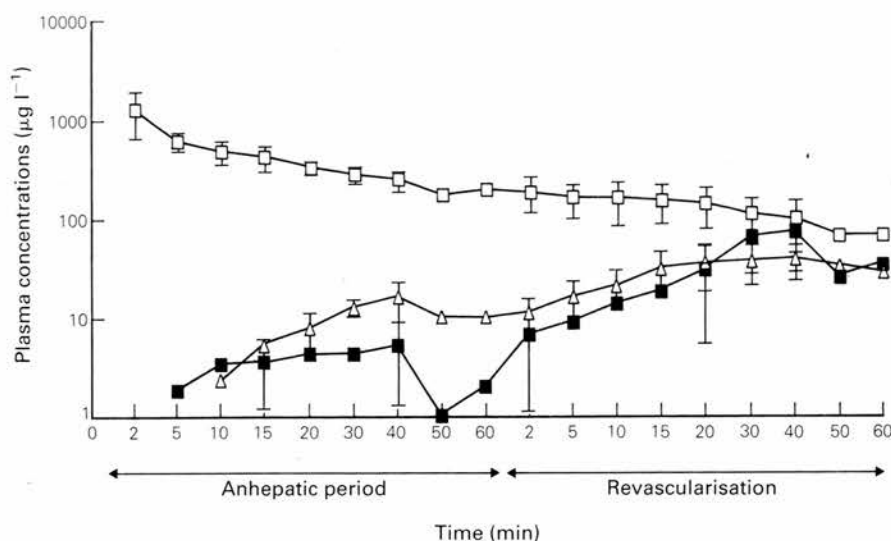


Figure 1 Plasma concentrations (mean \pm s.e. mean) of midazolam (\square), α -hydroxymidazolam (\triangle) and α -hydroxymidazolam glucuronide (\blacksquare) in five patients following administration of 10 mg of midazolam intravenously at the start of the anhepatic period of liver transplantation.

and the lung (Heizman *et al.*, 1983). Further studies are necessary to determine the exact site in the human and may be important to our understanding of the metabolic fate of this and other drugs in critically ill patients. The remaining patient (patient 1) had only low plasma concentrations of α -hydroxy midazolam glucuronide at the final two time points of the anhepatic period. Revascularisation of the donor liver appeared to correct this abnormality. This patient continued to be critically ill and subsequently died of an overwhelming viral infection precluding further studies.

Revascularisation of the liver was followed in all patients by significant increase in the plasma concentrations of midazolam metabolites. Patient 1 showed a similar rise in plasma concentrations of metabolites to the other patients although the concentrations were always lower. This would be consistent with the transplanted liver containing the normal amount or type of enzyme responsible for the metabolism of midazolam. Although the number of time points are too few to make definite conclusions the elimination half-life of midazolam (0.52 ± 0.23 h) appeared to be shorter than seen in healthy volunteers (Brown *et al.*,

1979; Dundee *et al.*, 1980, 1986; Greenblatt *et al.*, 1981 and 1984). The duration of the anhepatic period is necessarily short and the calculated half-life may therefore represent a distribution rather than an elimination half-life.

Caution in the application of these results to patients with severe liver failure is necessary. Although the failure of hepatic metabolism may be partly offset by activity at extrahepatic sites of metabolism, benzodiazepine receptors may be abnormally sensitive to the drug or its metabolite(s). Benzodiazepines used unnecessarily or incautiously, especially in repeated doses, may precipitate coma in patients with severe liver disease. When they are indicated, small doses must be titrated carefully to the needs of the individual patient.

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The pharmacokinetics of midazolam following orthotopic liver transplantation

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Seven patients with chronic liver disease received a 10 mg intravenous bolus dose of midazolam immediately following orthotopic liver transplantation. Plasma samples were analysed for midazolam and α -hydroxymidazolam by gas chromatography with electron capture detection. Data from three patients could not be evaluated. In the remaining four patients the pharmacokinetics of midazolam were essentially normal but the plasma concentrations of α -hydroxy-midazolam were higher than those found in healthy subjects. All patients required further sedation between 0.5 and 5 h later indicating that the duration of action of midazolam was not prolonged. These results suggest that following liver transplantation, patients have considerable drug metabolising capacity either in the liver or at extrahepatic sites.

Keywords midazolam pharmacokinetics liver transplant

Introduction

Midazolam is a benzodiazepine available as a water soluble salt suitable for parenteral administration. In normal subjects, it is metabolised to compounds which are rapidly cleared from the body. These attributes have prompted its use as a sedative in patients requiring intensive care, usually in combination with an opioid (Lloyd-Thomas & Booker, 1986; O'Dea & Hopkinson, 1987).

Following its use in critically ill patients, however, there have been reports of a prolonged duration of action (Byatt *et al.*, 1984; Byrne *et al.*, 1984; Dundee *et al.*, 1984). Since midazolam is believed to be metabolised in the liver (Allonen *et al.*, 1981), its deranged pharmacodynamics and pharmacokinetics in critically ill patients may be due to a failure of hepatic metabolism of the drug (Dundee *et al.*, 1986). A recent prospective study demonstrated a reversible inhibition of midazolam metabolism in the critically ill and suggested that this was due to reduced organ perfusion (Shelly *et al.*, 1987a). Studies in patients with chronic liver disease have given conflicting results about the effects of midazolam (Hamdy *et*

al., 1986; Binetti *et al.*, 1985; MacGilchrist *et al.*, 1986). The extrapolation of results from patients with chronic liver disease to patients who have suffered acute liver injury may not be valid and acute hepatic dysfunction, following disease or surgery, is more commonly seen in patients receiving intensive care. In order to clarify this point, patients were investigated following orthotopic liver transplantation. The donor liver for these patients is exposed to two major surgical procedures, removal from the donor and transplantation into the recipient. In addition, the metabolic function of the graft liver may be impaired by the period of ischaemia that is inevitable between these operations and, as a result, the transplanted liver is acutely and profoundly insulted. Postoperatively, transplanted patients require a period of controlled ventilation with appropriate sedation and analgesia. Since it is our usual practice to sedate these patients with intravenous bolus doses of midazolam (Shelly *et al.*, 1987b), this offered the opportunity to study the pharmacokinetics of midazolam in patients with acutely deranged liver function.

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Method

The study was approved by the Hospital Ethics Committee and informed consent was obtained from seven subjects preoperatively. Both the anaesthetic and surgical techniques have been described previously (Calne, 1987). During the study period the care of the patient was along conventional lines (Shelly *et al.*, 1987b) with the exception that sedation was provided by intermittent bolus doses of diazepam and morphine as required.

Postoperatively the patient was transferred to the intensive care unit and when haemodynamic stability had been achieved a baseline blood sample was taken from an intra-arterial line sited as part of the operative procedure. Midazolam hydrochloride (10 mg) was diluted to 10 ml with 0.9% saline and injected over 2 min through a centrally placed venous catheter. Arterial blood was sampled at 2, 5, 10, 15, 30, 45, 60 min and 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 12, 18, 24 h after the injection of drug. At each sampling time, 10 ml of blood was removed, placed in a tube containing an oxalate anticoagulant and mixed. The tubes were centrifuged at 3,000 rev min⁻¹ and the supernatant plasma removed and stored at -20°C until analysis by gas liquid chromatography (Heizmann & von Alten, 1981).

Drug and metabolite concentrations were measured relative to standard curves containing 50–1000 ng ml⁻¹ midazolam and 25–375 ng ml⁻¹ α -hydroxymidazolam. Mean precisions for the standards were $\pm 8.4\%$ and $\pm 7.4\%$, respectively and virtually identical values were found for quality assurance samples ($n=20$) containing 250 ng ml⁻¹ and 125 ng ml⁻¹ of midazolam and α -hydroxymidazolam, respectively. The latter were prepared and included in every analysis, and mean accuracies of the quality assurance samples were within 5% of the prepared values.

Pharmacokinetic parameters were calculated by model independent analysis. Plasma concentrations immediately after dosing ($C(0)$) were determined by back-extrapolation of the log-linear line for samples collected during the first 10–15 min after dosing. The initial volume of distribution (V_1) was then calculated from $\text{Dose}/C(0)$. Elimination half-lives ($t_{1/2}$) were estimated from the log-linear decline of the last four or five measurable plasma drug concentrations. Areas under the plasma drug concentration – time curves (AUC) were calculated by linear trapezoidal analysis between all samples that contained measurable midazolam concentrations. Values for the initial and terminal

proportions of the curve were then determined by addition of $(C(0) + C(2))/60$ and $Ct \times t_{1/2/0.693}$, respectively, where Ct was the last measured concentration. Clearance (CL) was calculated from Dose/AUC .

Results

Analysis of the plasma from three of the patients revealed interference with the assay probably from temazepam used as premedication. This rendered pharmacokinetic interpretation impossible and these patients have, therefore, been excluded from further consideration. The details of the remaining four patients including their postoperative liver function tests are shown in Table 1. All had impaired liver function in the postoperative period. The unusually low alanine transferase of patient 3 subsequently rose rapidly and may represent a spurious result. No delayed awakening was seen in the patients studied; all patients required further sedation at a mean time of 2 h (range 0.5–5 h).

The derived pharmacokinetic parameters for midazolam and α -hydroxymidazolam are shown in Table 2 together with values from normal subjects (Allonen *et al.*, 1981; Heizmann *et al.*, 1983). It was only possible to calculate approximate values for the parameters describing the distribution and elimination of midazolam in these patients owing to the biphasic decline and the relatively small number of data points obtained. The pharmacokinetic parameters estimated for midazolam were similar to those obtained from healthy volunteers. However, the plasma concentrations of α -hydroxymidazolam were higher than expected following intravenous administration of a 10 mg bolus of midazolam. In healthy volunteers, the mean maximum plasma concentration (mean C_{max}) of α -hydroxymidazolam is approximately 0.076 (Heizmann *et al.*, 1983) of the mean C_{max} of midazolam following intravenous administration of midazolam. In our patients, the ratio obtained using the same method of calculation was 0.18. Half-lives for the metabolite could not be determined owing to the multiphasic nature of its plasma concentration – time curve.

Discussion

Few agents are currently available for the sedation of patients receiving intensive care. Intravenous midazolam has been used (Lloyd-

Table 1 Details of the patients studied

	Patient				Normal range
	1	2	3	4	
Age (years)	42	40	49	18	
Sex	M	M	F	M	
Weight (kg)	53.3	75.0	50.0	66.0	
Diagnosis	Chronic acute hepatitis	Chronic rejection (RT)	Polycystic disease	Chronic rejection (RT)	
Bilirubin ($\mu\text{mol l}^{-1}$)	52	484	145	220	2-17
ALT (U l^{-1})	840	>1200	20	500	7-40
AP (U l^{-1})	62	231	43	652	30-135

RT = Retransplantation

ALT = Alanine transaminase

AP = Alkaline phosphatase

Table 2 The pharmacokinetic parameters for midazolam and α -hydroxymidazolam for the individual patients. The normal values are from Allonen *et al.* (1981) and Heizmann *et al.* (1983)

	Patient				Normal values
	1	2	3	4	
<i>Midazolam</i>					
$C(0)$ (ng ml ⁻¹)	950	800	600	—	
V_1 (l)	11	13	17	—	21 ± 7
$t_{1/2}$ (min)	80	30	55	105	137 ± 26
CL (l h ⁻¹)	20	38	32	18	19 ± 5
<i>α-hydroxymidazolam</i>					
C_{max} (ng ml)	62	124	219	123	24
AUC (ng ml ⁻¹ h)	66	122	120	103	42
t_{max} (h)	0.17	0.17	0.08	0.50	0.28

— Not calculated

 $C(0)$ Plasma concentration at time 0 $t_{1/2}$ Approximate elimination half-life calculated from the last 4-5 measurable time points and quoted to the nearest 5 min V_1 Volume of distribution of the central compartment

CL Total clearance

 C_{max} Maximum plasma drug concentration

AUC Area under the plasma drug concentration-time curve

 t_{max} Time to reach maximum drug concentration

Thomas & Booker, 1986; O'Dea & Hopkinson, 1987; Park *et al.*, 1986) but concern has been expressed regarding the occasional delayed recovery of critically ill patients following its administration (Byatt *et al.*, 1984; Byrne *et al.*, 1984; Dundee *et al.*, 1984). This has been attributed to impaired metabolism resulting in slow clearance of the parent drug. Midazolam is metabolised by hydroxylation and subsequent conjugation with glucuronic acid before excretion in the urine (Allonen *et al.*, 1981). The cytochrome P450 system is thought to be involved in its biotransformation and because of the extensive first pass metabolism of midazolam following oral administration, the liver is thought to be the site of metabolism (Allonen *et al.*, 1981; Dundee *et al.*, 1986). The explanations offered for the impaired metabolism of midazolam include a congenital impairment of cytochrome P450 function (Dundee *et al.*, 1986), or a reduced organ perfusion secondary to sepsis (Shelly *et al.*, 1987a).

Studies of the pharmacokinetics and pharmacodynamics of other benzodiazepines in patients with liver disease suggest that those benzodiazepines undergoing predominantly phase I metabolism, such as diazepam, tend to be profoundly affected by liver disease (Reeves, 1981; Klotz *et al.*, 1975) whilst those undergoing mainly conjugation reactions, such as temazepam, are relatively spared (Ghabrail *et al.*, 1986; Ochs *et al.*, 1986). In addition, the clearance of benzodiazepines undergoing phase I reactions is decreased by the concomitant administration of cimetidine, which is thought to act as an enzyme inhibitor; benzodiazepines metabolised by phase II reactions are unaffected by cimetidine (Klotz & Reimann, 1980 a,b).

Midazolam does not fit into this pattern. It undergoes predominantly phase I metabolism and, therefore, its pharmacokinetics would be expected to be affected profoundly by liver impairment. The pharmacokinetic profile of oral midazolam in patients with compensated cirrhosis is similar to that of healthy volunteers (Binetti *et al.*, 1985). Only in patients with severe cirrhosis are the pharmacokinetics and pharmacodynamics of midazolam affected (Hamdy *et al.*, 1986; Binetti *et al.*, 1985; McGil-

christ *et al.*, 1986). In addition, the pharmacokinetics of midazolam are not influenced by cimetidine as are those of diazepam (Greenblatt *et al.*, 1986). Since patients with liver impairment retain considerable metabolic capacity for midazolam, this suggests that its metabolism differs in some way from the phase I metabolism of other benzodiazepines. It may be that the enzymes responsible for the metabolism of midazolam are particularly resistant to damage or that they occur in extrahepatic sites. Extrahepatic metabolism of lorazepam has been postulated in dogs (Gerken *et al.*, 1981).

Liver transplantation can be considered as a severe, acute hepatic injury. Our patients studied under these conditions demonstrated normal pharmacokinetics of midazolam but with a higher than normal plasma concentration of α -hydroxymidazolam, the primary metabolite. The increased plasma concentrations of α -hydroxymidazolam may be due either to an increased rate of formation of the metabolite or to a reduced rate of conjugation to the glucuronide. Since the pharmacokinetics of midazolam appeared normal, the latter is more likely. This could have been confirmed by measuring the plasma concentrations of the secondary metabolite α -hydroxymidazolam glucuronide but this assay was not available at the time of the study.

The pharmacokinetic data obtained from this study were limited because of the small numbers of patients and data points. However, the fact that the initial metabolism of midazolam to α -hydroxymidazolam was not substantially impaired suggests that following liver transplantation patients retain considerable metabolic capacity for midazolam either within the newly transplanted liver or at extrahepatic sites. In addition the results demonstrate that midazolam does not have a prolonged duration of action in these patients.

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Extra-hepatic metabolism of midazolam

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Six patients received 10 mg of midazolam intravenously during the anhepatic period of liver transplantation. Arterial blood was sampled during this time and for a similar period following revascularisation. The plasma was analysed using gas chromatography and electron capture detection (GC-ECD) for midazolam α -hydroxymidazolam and α -hydroxymidazolam glucuronide. Five of the six patients had small but significant concentrations of metabolites detected during the anhepatic period, demonstrating the presence of extra-hepatic sites of metabolism for this drug. The remaining patient had plasma concentrations of metabolites below the lower limit of detection ($2\mu\text{g l}^{-1}$). This may represent a pharmacogenetic abnormality or a temporary failure of midazolam metabolism secondary to the patients illness affecting the extra-hepatic sites of metabolism.

Keywords midazolam extra-hepatic metabolism

Introduction

Midazolam is a short acting benzodiazepine and is commonly used to sedate patients requiring brief procedures, to induce anaesthesia and for prolonged sedation during intensive care. It is hydroxylated by the cytochrome P450 system predominately to α -hydroxymidazolam, which has some pharmacological activity, and to a smaller extent to 4-hydroxymidazolam, which is thought to be inactive. Following this, glucuronidation occurs making the compound more water-soluble and allowing renal elimination. In the postoperative period prolonged sedation has been observed (Byatt *et al.*, 1984; Byrne *et al.*, 1984). A reversible failure of metabolism has been demonstrated in patients with sepsis (Shelly *et al.*, 1987) and in a child with acute derangement of liver function following cardiac surgery (Lloyd-Thomas & Booker, 1986). These observations prompted a study on the pharmacokinetics of midazolam in patients following orthotopic liver transplantation (when liver function is deranged due to cold injury, ischaemia and the effects of surgery and anaesthesia following the donor operation and the liver transplant procedure). This study demonstrated normal pharmacokinetic parameters for the parent

drug but the plasma concentrations of the α -hydroxy product were surprisingly high (Shelly *et al.*, 1989).

When orthotopic liver transplantation is performed there is a period of no liver function. This enables the importance of the liver in the metabolism of a drug to be investigated. Several phases in the surgical procedure can be identified. Firstly, the diseased liver is dissected leaving it with its vascular connections intact (skeletonisation). This is followed by clamping of all of the hepatic vessels and removal of the diseased liver, after which the suprahepatic inferior vena cava of the donor liver is anastomosed to the recipient's vena cava and the portal vein or the infra hepatic cava of the donor liver anastomosed to the recipient's vessel (anhepatic period). When these anastomoses are complete the vascular clamps are released (revascularisation). The remaining anastomoses are completed (hepatic artery, portal vein or inferior vena cava), the biliary conduit is fashioned and the abdomen is closed (Calne, 1987). The anhepatic period provides a unique opportunity to study the metabolism of drugs in man. Studies during this period have not been performed previously because of the many

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Investigation of the spontaneous modes of breathing of different ventilators

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Abstract. We investigated six ventilator systems which were designed to allow spontaneous breathing. The time delay between initiation of inspiratory effort and the beginning of inspiratory gas flow was measured, as was the amount of negative (to ambient) pressure generated in the airway needed to produce the gas flow. We found that the flow-by program of the Puritan-Bennett 7200 caused minimal time delay and virtually no negative pressure was required to instigate gas flow. This should be contrasted with the other ventilator systems, which caused significant delay and inspiratory effort and hence increased work of breathing.

Key words: Spontaneous breathing – Ventilators – Work of breathing – Inspiratory pressure support – Flow-by systems – IMV circuits

In 1982 Gibney, Wilson, Pontoppidan, and subsequently other workers [1, 4, 6, 7, 10, 14] pointed out that ventilator systems based on a demand valve create an inspiratory resistance to spontaneous breathing which is unacceptable in clinical practice. All authors have suggested alternative sources of fresh gas supply based around an IMV one-way valve and reservoir bag, as illustrated in Figure 1. Various authors have estimated the work of breathing using either the demand valve systems or modifications of the circuit described above. The work of breathing was found to be excessive through the demand valves when compared to that measured using the continuous flow systems [6, 10]. Prior to this, in 1979, Gherini [5] showed that the inspiratory work of breathing on CPAP increased if the airway pressure decreased during inspiration.

Since the early 1980's, the continuous flow system illustrated above (Fig. 1) has been in use in the Royal Free Hospital Intensive Therapy Unit and has proved

clinically acceptable during the weaning of over 600 patients. Among reasons for its success are that there is minimal time delay between the instigation of inspiratory effort and the start of gas flow, and that the theoretical peak inspiratory flow is instantly available and far in excess of that which most patients requiring IMV could achieve. When used in conjunction with CPAP, the bag is stretched tightly and it is this tightness which has been thought to deliver a degree of inspiratory pressure support, leading to a reduction in the inspiratory work of breathing.

Manufacturers of ventilators have recognised the disadvantages of the demand valve systems and the last few years have seen the widespread introduction of systems with inspiratory assistance (pressure support) for the spontaneous phase of IMV. Whilst this will undoubtedly reduce the inspiratory work of breathing and thus the oxygen consumption [2, 8], the sensitivity of the ventilator to the inspiratory effort is still critical if no time delay before the onset of gas flow is to occur. The most recent attempt to further reduce the inspiratory work of breathing during the spontaneous phase has been the introduction of "flowby" on the Puritan-Bennett 7200.

The observed clinical advantages of the continuous flow systems led us to this investigation of recently introduced breathing systems using, variously, inspiratory pressure support (Siemens Servoventilator 900C, Engstrom Erica, Puritan-Bennett 7200, Drager EV-A) and continuous flow systems (Modified Siemens Servoventilator 900B, Puritan-Bennett 7200 flow-by).

Materials and methods

The changes in airway pressure, gas flow rates and inspiratory time lag were measured in the following systems:

been compromised by surgery or sepsis. It may, however, have contributed to the ischaemic changes seen.

Active peristalsis is a known feature of vasopressin administration and previous reports have described vomiting, diarrhoea and abdominal discomfort among its side effects [2, 6, 24]. The rise in core temperature during vasopressin administration was a constant finding. In no patient did core temperature fall. The corresponding rise in peripheral temperature suggests that this is not due to central diversion of blood flow with peripheral vasoconstriction but may be the result of increased heat production.

Conclusion

Vasopressin controlled intra-abdominal bleeding in four critically ill patients and reduced the rate of bleeding in two others. The physiological effects of vasopressin vary between patients but there was a general improvement in haemodynamic parameters and six patients had a diuresis following its administration. Vasopressin may be useful in the management of patients with massive and uncontrolled intra-abdominal bleeding. However, because of the risk of ischaemic damage to other organs, vasopressin should only be used when conventional medical and surgical therapy has failed.

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tachyphylaxis. In patient 8 the infusion was continued at the same rate after bleeding was eventually controlled in an attempt to allow haemostasis but after 12 h, bleeding restarted with the infusion still in progress. Patient 9 required increasing doses of vasopressin to control his bleeding and when the infusion rate was reduced, bleeding restarted.

Discussion

There have been a number of reports of the efficacy of vasopressin in the control of bleeding, particularly from oesophageal varices [2, 6, 9]. These have stressed the haemostatic effect of vasopressin and mentioned various side effects. The group of patients reported here had massive intra-abdominal bleeding uncontrolled by conventional treatment. While the haemostatic effect of vasopressin was the primary objective of treatment, the intensive monitoring of these patients during treatment enabled documentation of the physiological effects of vasopressin in critically ill patients during haemorrhage.

Vasopressin is a powerful vasoactive substance, known to decrease splanchnic blood flow [10] and thought to act by constriction of splanchnic arteriolar sphincters [11, 12]. The haemostatic effect of vasopressin is, however, variable [9, 13, 14]. This has been attributed to individual differences in hepatic blood flow characteristics and hepatic function [9, 12] and vasopressin may be more effective in critically ill patients [9]. The results from this group compare favourably with other reported series [5, 11]. Vasopressin may, therefore, be used together with laparotomy in the management of patients with uncontrolled intra-abdominal bleeding following major abdominal or hepatic surgery. A response to an initial bolus dose of vasopressin may indicate a more sustained response to its infusion. However, continued bleeding requiring a prolonged infusion of vasopressin indicates a poor response and increases the risk of complications. The high mortality rate seen in this group of patients reflects their severe illness and the influence of vasopressin cannot be determined accurately.

Patient 3 was the only patient who did not respond at all to vasopressin; she continued to bleed from the liver surface following an emergency partial hepatectomy for bleeding into a hepatoma. Patient 4 had similar bleeding following a partial hepatectomy for a hepatoma but he responded well to vasopressin. An important difference between these patients was that patient 4 had a patent portal vein but the portal vein of patient 3 was occluded by tumour. The entire hepatic blood supply of patient 3 was, therefore,

through her left hepatic artery (the right lobe of the liver having been surgically removed). While portal venous pressure decreases in response to vasopressin, the response of the hepatic artery is different, a biphasic response having been demonstrated in dogs [15, 16]. Initially hepatic arterial flow decreases but this rapidly reverses so that 15–20 min after administration of vasopressin, hepatic artery flow is double the control value. The failure to achieve haemostasis in patient 3 may result from an increased hepatic arterial flow in response to vasopressin. Similar bleeding in patient 4 responded to vasopressin since he had a patent portal vein and total hepatic blood flow decreased.

The hypertensive effects of vasopressin have been previously reported in patients with oesophageal varices [11–13, 15]. The increase in mean arterial pressure and central venous pressure and the decreased heart rate seen in these patients at the start of vasopressin administration, may be due to the autotransfusion effect of splanchnic vasoconstriction, since the splanchnic vascular bed is a significant blood reservoir [17].

When mentioned at all, previous studies have reported an antidiuretic effect of vasopressin [15] and normally release of vasopressin from the posterior pituitary causes an increase in renal tubular reabsorption of water. All the patients reported here had impaired renal function before treatment with vasopressin; the impressive diuresis experienced by five patients is, therefore, all the more significant and no patient became anuric. The mechanism for this increased urine output is unknown but may be related to an increased renal perfusion pressure with the increased mean arterial pressure.

Myocardial ischaemia has been reported following vasopressin [19] and it has been used as a stress test to provoke ischaemic changes [20]. Dysrhythmias related to vasopressin administration were seen in three patients. In addition, diffuse myocardial myocytolysis was found at post-mortem examination in two other patients; this is a non-specific change but vasopressin may have contributed to its development.

Intestinal ischaemia has been described following infusion of vasopressin into the superior mesenteric artery [21–23] but not following intravenous administration. The pancreatic and mucosal lesions are unlikely to have been due entirely to vasopressin, although it may have contributed to their development. The third patient had an infarcted appendix following prolonged vasopressin infusion and this would seem to be attributable to vasopressin.

Hepatic ischaemia has not been described before and in this study vasopressin cannot be conclusively incriminated since all the patients had livers that had

decreased during treatment but this change did not reach statistical significance and a tachycardia returned upon its cessation. The changes in central venous pressure were less marked; a transient but statistically significant rise ($p < 0.05$) coincided with the decreased heart rate on starting the infusion.

Urine output

The urine output of individual patients for the 4-hour period before vasopressin treatment compared with the 4-h period immediately after, is shown in Table 3. Although the overall changes fail to reach statistical significance, they were of clinical significance. All patients initially had impaired renal function but five (patients 1, 2, 3, 9, 10) had a prompt diuresis when vasopressin was initiated. Patient 4 had a diuresis when started on a vasopressin infusion following bolus dosage and patient 6 had had a significantly improved urine output since commencement of an adrenaline infusion the previous day.

Ischaemia

Myocardial. Dysrhythmias were documented electrocardiographically in three patients during vasopressin treatment. Patient 2 had an episode of supraventricular tachycardia patient 8 a period of bradycardia and patient 9 bradycardia together with ventricular ectopic beats. All these changes disappeared when the rate of infusion was decreased. In patients 1 and 5 diffuse myocardial myocytolysis was noted at post-mortem examination.

Intestinal. Three patients had evidence of bowel ischaemia. Patient 1 had pancreatic infarction and patient 2 colonic ulceration. Patient 9, after a vasopressin infusion lasting 124 h, was found to have an infarcted appendix which was removed.

Hepatic. Four patients had some evidence of hepatic ischaemia. Patient 1 had areas of recent infarction 13 days after vasopressin administration, patient 2 had centrilobular necrosis, patient 8 had discrete areas of infarction and patient 5 had ischaemic necrosis.

Gastrointestinal motility

All the patients had an ileus immediately prior to treatment, nevertheless evacuation of bowel motions occurred in three patients (patients 1, 9, 10) and the volume of nasogastric aspirate increased in patients 5 and 7. Patient 1 was in hepatic coma and in an attempt to improve her conscious level, she had a 4-l enema before vasopressin treatment. The enema had been unproductive but vasopressin caused a prompt evacuation of her bowels and a slight improvement in her conscious level.

Other physiological effects

Temperature changes. The changes in core temperature, rectal or axillary, for the 4-h periods before and after starting vasopressin and before and after its cessation, are shown in Figure 2. The increase in core temperature with the start of vasopressin infusion was statistically highly significant ($p < 0.0005$). In three patients, the core to peripheral temperature difference was monitored and remained unchanged.

Pulmonary arterial pressures. Pulmonary arterial pressures were measured in two patients. In one, both pulmonary artery systolic and diastolic pressures rose with intermittent administration of vasopressin returning to baseline levels between doses. In the other patient pulmonary arterial pressures remained unchanged.

Tachyphylaxis. Two of the patients who received prolonged vasopressin infusions appear to have shown

Table 3. Urine output for individual patients for the 4-h period before vasopressin compared with the 4-h period immediately after

Patient number	4 h before vasopressin	4 h after vasopressin	Change (%)
1	48	141	194
2	45	105	133
3	43	165	284
4	84	75	-11
5	0	8	
6	214	250	17
7	38	34	-11
8 ^a	26	22	-15
9	50	101	102
10	164	470	187

^a Figures for 1 h before and after vasopressin

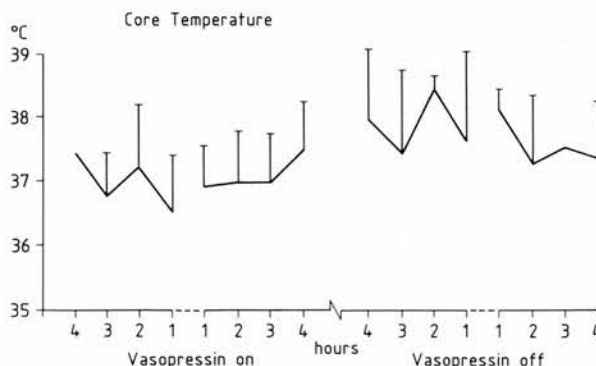


Fig. 2. Core temperature, mean and standard deviation, for 4-h periods before and after commencement and cessation of vasopressin infusion

Table 2. Blood loss during the 4-h period before vasopressin administration compared with the 4-h period immediately after, together with vasopressin dosage for individual patients in chronological order and the outcome of their bleeding

Patient number	4 h before vasopressin	4 h after vasopressin	Decrease in blood loss (%)	Vasopressin treatment	Bleeding controlled
1	750	360	52	20 units bolus \times 2	Vasopressin alone
2	845	445	47	20 u/h infusion 14 h	Vasopressin following laparotomy
3	5459	5865	+ 7	10 units bolus \times 2 20 units bolus \times 1	Not controlled
4	2495	1460	42	20 units bolus \times 1 10 u/h infusion 12 h	Vasopressin following laparotomy
5	3500	3040	13	12–24 u/h infusion 10 h	Laparotomy following vasopressin
6	600	500	17	2.5–10 u/h infusion 90 h	Not controlled
7	1593	966	40	10 u/h infusion 4 h	Laparotomy following vasopressin
8 ^a	325	170	48	20 units bolus \times 1 1–10 u/h infusion 132 h	Not controlled
9	945	730	23	2–7 u/h infusion 124 h	Vasopressin following laparotomy
10	165	144	13	5–10 u/h infusion 12.5 h	Laparotomy following vasopressin

^a Figures for 1 h before and after vasopressin. u/h = units/hour

minimal response to vasopressin. Patients 5 and 10 bled following hepatic retransplantation and their bleeding was eventually controlled surgically. Patients 6 and 9 had intra-abdominal sepsis and haemostasis was difficult to achieve in spite of prolonged vasopressin infusions and repeated surgical exploration; bleeding was eventually controlled by vasopressin in patient 9.

Mortality

Patients 7 and 10 survived and were discharged from hospital. The three patients with bleeding uncontrollable by vasopressin or laparotomy, died of their intra-abdominal bleeding within 24 h of cessation of the vasopressin infusion. Patient 2 died of unrelated colonic bleeding, 18 days after control of his intra-abdominal bleeding by vasopressin. The other patients died of multisystem failure 15.2 ± 4.1 days (mean \pm SD) after receiving vasopressin.

Cardiovascular parameters

Changes in mean arterial pressure, heart rate and central venous pressure for periods before and after commencement and cessation of vasopressin infusion are shown in Figure 1. Mean arterial pressure increased significantly ($p < 0.025$) with the start of the infusion but returned to baseline values when the infusion was stopped. A tachycardia was present in all patients before administration of vasopressin. Heart rate

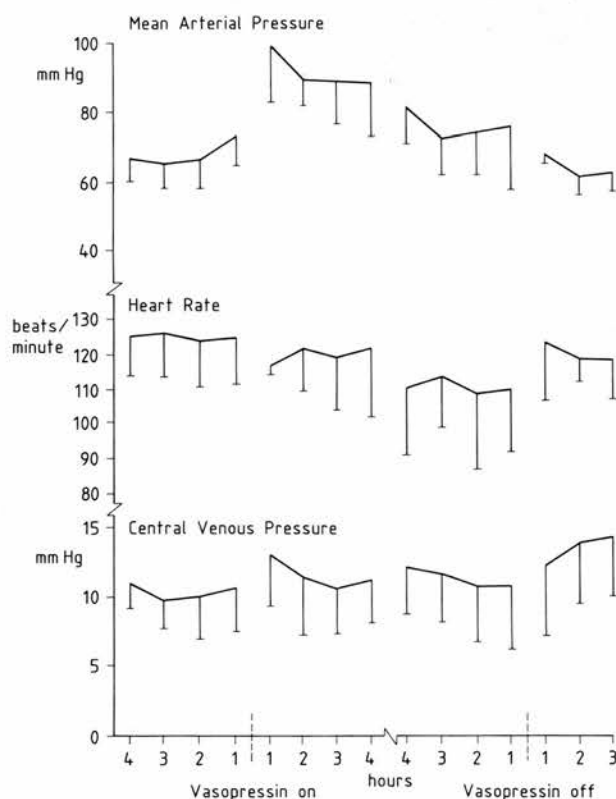


Fig. 1. Mean arterial pressure, heart rate and central venous pressure for 3-h periods before and after commencement and cessation of a vasopressin infusion. Mean and standard deviation for all values are shown

tients were receiving artificial ventilation. All were receiving infusions of fresh frozen plasma and platelet concentrates as well as calcium supplements but none had disseminated intravascular coagulopathy.

Arterial pressure and central venous pressure were measured directly via intra-arterial and central venous catheters; in addition, a continuous electrocardiogram, core temperature, urine output and nasogastric drainage were monitored in all patients. Additional parameters were measured as indicated. Hourly blood loss was calculated from measurements of external blood loss. The volume of blood and colloid required to maintain cardiovascular stability was recorded and any adverse effects of vasopressin noted. The records of post-mortem examinations, performed on six of the patients, were reviewed. Student's paired t-test was used to compare results where appropriate.

Vasopressin was diluted in 5% Dextrose to form a solution containing 1 or 2 units/ml and administered using an accurate syringe driver. The dose administered was similar to that used for the treatment of oesophageal varices [5, 6] since the detailed pharmacokinetics of exogenous vasopressin have not been evaluated.

Results

The details of the patients and their surgical treatment before vasopressin was administered are shown in Table 1. The total duration of bleeding was 32.9 ± 17.3 h (mean \pm SD) with a measured non-operative blood loss of 10.5 ± 4.9 l and a blood transfusion requirement of 18.4 ± 11.2 l prior to vaso-

pressin treatment. In spite of the infusion of clotting factors and platelets, the prothrombin ratio was 1.5 ± 0.3 and the platelet count was $84.7 \pm 61.7 \times 10^9$ /ml.

Bleeding

External blood loss was used as an index of bleeding and the change in the measured loss, to assess response to vasopressin. Although occult losses are undetected, this provides an estimate of blood loss and follows the same trend as the change in transfusion requirement in individual patients. The estimated blood loss during the 4-hour period before giving vasopressin compared with the same period after its administration is shown in Table 2, together with vasopressin dosage for individual patients and the outcome of their bleeding.

In all but one of the patients blood loss fell following vasopressin and the overall decrease in blood loss was statistically significant ($p < 0.05$). Patient 1 had bleeding that was controlled by vasopressin alone, the remaining nine patients required additional haemostatic laparotomy. Four (patients 2, 3, 4, 9) had undergone recent laparotomy for haemostasis before starting vasopressin and although specific bleeding points were controlled, massive haemorrhage continued. Bleeding was controlled by vasopressin in three of the four, in patient 3 it was uncontrolled. The remaining patients were treated with vasopressin without prior laparotomy and all required subsequent laparotomy for haemostasis. In two of these patients (patients 7, 8), bleeding was reduced preoperatively increasing the time available for preparation. Four patients had a

Table 1. Details of patients in chronological order who received vasopressin and their surgical management before vasopressin treatment

Patient number	Age (years)	Sex	Weight (kg)	Diagnosis	Bleeding source	Surgical management
1	14	F	59	Chronic active hepatitis	Gastric erosions	Liver transplantation
2	57	M	67	Alpha-1-antitrypsin deficiency	Peritoneum	Liver transplantation, laparotomy
3	15	F	45	Hepatoma	Liver, into necrotic tumour	Partial hepatectomy, laparotomy
4	60	M	78	Hepatoma	Liver	Partial hepatectomy, laparotomy
5	22	F	46	Chronic rejection	Liver and arteries near adrenal and oesophago-gastric junction	Liver retransplantation
6	39	M	65	Intra-abdominal sepsis	Peritoneum	Drainage of abscesses
7	23	M	76	Budd Chiari	Artery inferior to liver	Liver transplantation
8	38	F	83	Wilsens disease	Artery in retroduodenal lymph node	Liver transplantation
9	50	M	68	Intra-abdominal sepsis	Peritoneum and liver	Drainage of abscesses, laparotomy
10	28	F	55	Hepatic failure	Retroperitoneal area	Liver retransplantation

The physiological effects of vasopressin when used to control intra-abdominal bleeding

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Abstract. Vasopressin was used in ten critically ill patients with massive intra-abdominal bleeding unresponsive to conventional therapy. Vasopressin controlled bleeding in four patients, three of whom had continued to bleed following laparotomy for haemostasis; in two other patients, bleeding was reduced. All the patients were intensively monitored throughout the period of the vasopressin treatment; this enabled other physiological effects of vasopressin to be documented and reported. Mean arterial pressure and central venous pressure increased following the administration of vasopressin and there was a decrease in heart rate. Core body temperature rose significantly. Although all the patients had impaired renal function before receiving vasopressin, five had a prompt diuresis following its administration. Eight patients died but only three of intra-abdominal bleeding; two patients survived to leave hospital. Four patients had post-mortem evidence of ischaemia in the heart, liver and gastrointestinal tract; vasopressin may have contributed to the development of this. Vasopressin may have a place in the management of patients with life-threatening intra-abdominal haemorrhage but its use should be confined to those patients in whom conventional therapy has failed.

Key words: Vasopressin – Abdominal bleeding – Cardiovascular measurements – Renal failure

Life threatening intra-abdominal bleeding is a rare event but when it does occur, it provides a challenge to all involved in its management. Advances in liver surgery have increased the frequency of major hepatic surgery and the incidence of intra-abdominal bleeding following this type of surgery has risen correspondingly. Since massive intra-abdominal bleeding is an im-

portant complication in a regional centre for liver transplantation and major liver surgery, we have been concerned with its control.

Vasopressin has long been known to reduce portal pressure [1] and this has led to its use in the control of bleeding particularly from oesophageal varices. Direct administration into the superior mesenteric artery has been used to produce local haemostasis and minimise systemic effects [2, 3], however, intravenous administration has the same haemostatic efficacy and systemic effects [3–5] and is considerably simpler. Intermittant bolus administration of vasopressin reduces bleeding from oesophageal varices [6, 7] but frequent short infusions [8] or a continuous infusion [4] may be more effective.

The ability of vasopressin to reduce pressure in the splanchnic vascular bed, prompted us to use vasopressin intravenously in an attempt to control intra-abdominal bleeding when conventional treatment proved ineffective.

Patients

All patients following liver transplantation or suffering from major intra-abdominal bleeding, are managed on the intensive care unit. Ten patients received vasopressin over an 8-year period and the case notes of these patients were reviewed retrospectively. Initially vasopressin was used in 3 patients following liver transplantation to control intra-abdominal haemorrhage when other therapeutic manoeuvres, including laparotomy, had failed. However, as experience with the drug grew it was used in patients with other causes of intra-abdominal bleeding.

All the patients were exsanguinating from their intra-abdominal bleeding and all had impaired renal function from prerenal failure or acute tubular necrosis; four were requiring haemodialysis. Nine pa-

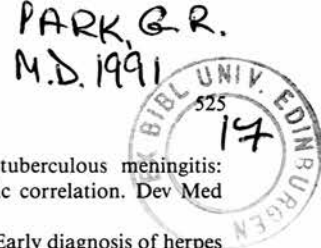
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Failure of critically ill patients to metabolise midazolam

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Summary

The pharmacokinetics of midazolam and its metabolite, 1-OH midazolam, were studied in six critically ill patients during and after a continuous intravenous infusion of midazolam. Four patients had an increased elimination half-life of midazolam; two were associated with a reduction in plasma clearance with low plasma concentrations of the metabolite, and two with normal metabolite levels and increased volume of distribution. The two patients with reduced clearance suffered from septic shock and were studied over a longer period. Their altered clearance was due to a reduced capability to form the 1-OH metabolite. As their condition improved, plasma concentrations of 1-OH midazolam increased and midazolam clearance returned towards normal. The impaired ability of critically ill patients with septic shock to metabolise midazolam, may be due to reduced organ perfusion and may lead to cumulation of midazolam in these patients.

Key words

Hypnotics, benzodiazepines; midazolam.

Pharmacokinetics.

Sedation of patients who require intensive care is necessary to reduce the distress of the patient and to facilitate treatment. Several agents are available but all have disadvantages when given continuously to critically ill patients. Accumulation of barbiturates may lead to prolonged sedation after the infusion has been discontinued. Chlormethiazole has been used¹ but the large fluid volume required may compromise fluid balance and nutrition. Etomidate and alphaxalone/alphadalone (Althesin) provide effective sedation when given by continuous infusion, but problems with their use have led to their being abandoned.²⁻⁴

Until the introduction of midazolam, benzodiazepines have not been used by continuous intravenous infusion because of the prolonged effect of the parent drug and, in some cases, of its pharmacologically active metabolites. Midazolam is a water soluble benzodiazepine with a rapid onset and a short duration of action in normal subjects.⁵ It has a short elimination half-life, a relatively large volume of distribution and a high plasma clearance.⁶ Its major metabolic pathway is hydroxylation and subsequent conjugation with glucuronic acid before elimination in the urine. Midazolam is thought to undergo biotransformation by the P450 system⁷

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and, since it undergoes extensive first pass metabolism following oral administration, the liver and gut wall are thought to be important sites of metabolism although other organs may also be involved. The 1-hydroxy metabolite of midazolam is pharmacologically active but has a shorter elimination half-life than midazolam itself.⁸

A prospective study was performed to investigate the pharmacokinetics of midazolam in critically ill patients. Prolonged sedation following continuous intravenous infusion of midazolam was reported⁹⁻¹¹ while this study was being planned, and the blood sampling protocol was extended in view of this.

Method

Six consecutive critically ill patients who had not received benzodiazepines since admission to the intensive care unit and who required sedation to facilitate controlled ventilation, received a continuous intravenous infusion of midazolam. Approval for the study was obtained from the district ethics committee. Informed consent was obtained from three of the patients themselves (patients C, D and E) but the remainder were unable to consent personally and informed consent for the study was then obtained from their relatives.

Midazolam hydrochloride was diluted with 5% dextrose to produce a solution that contained 1 mg/ml and administered through a centrally placed venous catheter. The rate of infusion was altered by the nursing staff subject to prescribed limits which were reviewed regularly by medical staff. No other benzodiazepines were administered during the study period.

Blood samples were withdrawn from an indwelling arterial line into tubes that contained oxalate anticoagulant, before the infusion was commenced and one hour after starting the infusion; thereafter daily blood samples were taken to ascertain whether steady state had been reached. Frequent blood samples were taken following cessation of the infusion, until the patient was clinically awake (Table 1). The blood was centrifuged and the supernatant plasma separated and stored at -20°C for analysis. Plasma concentrations of midazolam and the metabolite 1-OH midazolam were estimated by gas-liquid chromatography with electron capture detection.¹²

Table 1. Times of blood sampling during continuous intravenous infusion of midazolam.

Before administration of midazolam
One hour after commencement of infusion
Daily sampling at 10:00 hours
On cessation of infusion
Thereafter at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 hours
Six-hourly until the patient wakes

Pharmacokinetic parameters for midazolam were determined using standard, model-independent pharmacokinetic methods. It was assumed that a steady state would be reached if midazolam was infused continuously at the same rate for 15 hours or more.

The severity of the patients' illness was assessed by determination of their APACHE II score¹³ on admission to the intensive care unit and on the day of cessation of the midazolam infusion. The sepsis score¹⁴ was also calculated for each patient on admission and daily thereafter. Note was made of all other drugs administered to the patients, particularly other sedative and analgesic drugs and inotropic agents.

Throughout their period of intensive care, the conscious level of each patient was recorded every 2 hours using a sedation scoring system developed for routine use in this intensive care unit.¹⁵ This system uses six clinically identifiable end points; fully alert, roused by voice, roused by pain, unrousable, paralysed, or asleep. The time taken for the patients to wake following cessation of the midazolam infusion was noted from the recorded conscious levels and taken as the point where the patient became fully alert or increased their conscious level by at least two steps. The plasma concentrations of midazolam and of the metabolite 1-OH midazolam at the point of awakening were extrapolated from the graphs of plasma drug and metabolite concentrations against time.

Results

The details of the six patients are shown in Table 2. One patient failed to complete the protocol and a further patient was studied on two occasions. Patient E received an infusion of midazolam for 16 days to facilitate controlled ventilation. No samples were taken during the decline phase after cessation of the infusion but his results are included because of the duration of the infusion. In patient F, the infusion was discontinued on

Table 2. Details of the six patients studied.

Patient	Age (years)	Sex	Weight (kg)	APACHE II score *	Sepsis score *	Diagnosis
A	76	M	78	a 14 b 14	2 2	Prolonged postoperative neuromuscular blockade
B	68	M	66	a 20 b 17	6 5	Postcardiac arrest
C	54	F	60	a 8 b 3	0 3	Multiple trauma
D	62	M	70	a 16 b 17	12 10	Re-exploration of femoro-popliteal graft
E	60	M	60	a 30 b 32 c 26	20 18 13	Chronic myeloid leukaemia, septic shock
F	76	M	60	a 26 b 29 c 24	13 19 17	Postoperative respiratory failure, septic shock

* a, On admission; b, on day of cessation of midazolam infusion, except for patient E, day 4 scores; c, patient E, scores on day 14, patient F, scores on the second occasion when the midazolam infusion was stopped.

Table 3. The mean dose of midazolam, the duration of infusion and other sedative, analgesic and vasoactive drugs administered to each patient.

Patient	Mean dose (mg/hour)	Infusion duration (hours)	Analgesics	Vasoactive agents
A	2.7	10	Morphine	
B	6.4	26	Morphine	Dopamine Lignocaine Digoxin
C	3.4	143	Morphine	Dopamine
D	3.8	39	Morphine	Dopamine
E	7.0	369	Morphine Alfentanil Fentanyl	Dopamine Dobutamine Methoxamine Phenylephrine Digoxin Adrenaline Verapamil
F	4.6	159	Morphine Alfentanil	Dopamine Dobutamine Methoxamine Adrenaline Digoxin

the 5th day to assess the patient's conscious level but was restarted to control agitation. The infusion was finally stopped 3 days later to attempt weaning from controlled ventilation. Blood samples were taken on each occasion the infusion was stopped. All the patients except patients E and F survived to be discharged to the ward. Patient E died on his 20th day of intensive care, 5 days after his last dose of midazolam and patient F died on his 82nd day of intensive care, 75 days after his infusion ended; both died of multisystem failure. APACHE II and sepsis scores are shown for patient E on day 4 of his midazolam infusion, when he suffered from septic

shock, and on day 14, when clinical improvement was evident. The same scores are shown for patient F on both days his sedation was discontinued.

In all the patients, the infusion of midazolam was commenced shortly after their admission to the intensive care unit. The dose and duration of the infusions are shown in Table 3, together with other sedative, analgesic and vasoactive agents administered. None of the patients received other benzodiazepines or neuromuscular blocking agents during the study period. Concomitant drugs administered included antibiotics, steroids, heparin and diuretics. All patients

received ranitidine and morphine, which was administered by intravenous bolus dosage or by continuous intravenous infusion. Dopamine was given by continuous intravenous infusion to all but patient A. Patients A and C had normal renal function, patients B and D had impaired renal function whilst patients E and F were in renal failure. Only patients E and F had impaired liver function and reduced serum albumin concentrations.

The derived pharmacokinetic parameters are shown in Table 4, together with the normal values.^{16,17} One patient (C) had normal pharmacokinetic parameters and in another (A), the data were incomplete but appeared normal. The remaining patients had prolonged elimination half-lives as a result of reduced clearance of midazolam. In two cases (patients B and D), plasma concentrations of 1-OH midazolam were normal and the increased half-life was due partly to an increased volume of distribution.

Two patients (E and F) initially had a reduced clearance of midazolam with increasing plasma concentration of midazolam during the period of

Table 4. Pharmacokinetic parameters for midazolam in each patient.

Patient	Clearance (litres/kg/hour)	Half-life (hours)	Volume of distribution (litres/kg)
Normal range ^{16,17}	0.24–0.71	0.84–5.4	0.86–1.86
A	*	2.5	*
B	0.11	13.9	2.23
C	0.42	2.5	1.51
D	0.06	18	High†
E a	0.04	*	*
b	0.49		
F a	0.03	21	0.88
b	0.08	7.8	0.98

* No values: patient A, not at steady state when infusion discontinued; patient E, no samples during decay from plateau level.

† Clearance at steady state probably reduced due to interfering peak in predose sample.

a, Patient E, day 4, patient F, first cessation of midazolam infusion; b, patient E, day 14, patient F, second cessation of midazolam infusion.

their infusion and low or absent plasma concentrations of 1-OH midazolam. As their condition improved, plasma concentrations of midazolam

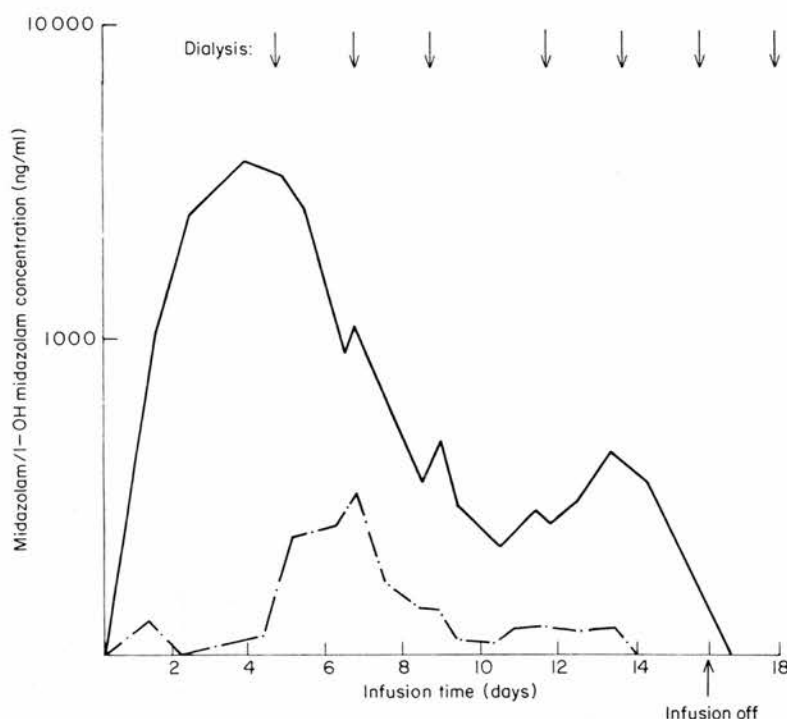


Fig. 1. Plasma midazolam and 1-OH midazolam concentrations for patient E throughout the period of study. —, Plasma midazolam concentration; ---, plasma 1-OH midazolam concentration.

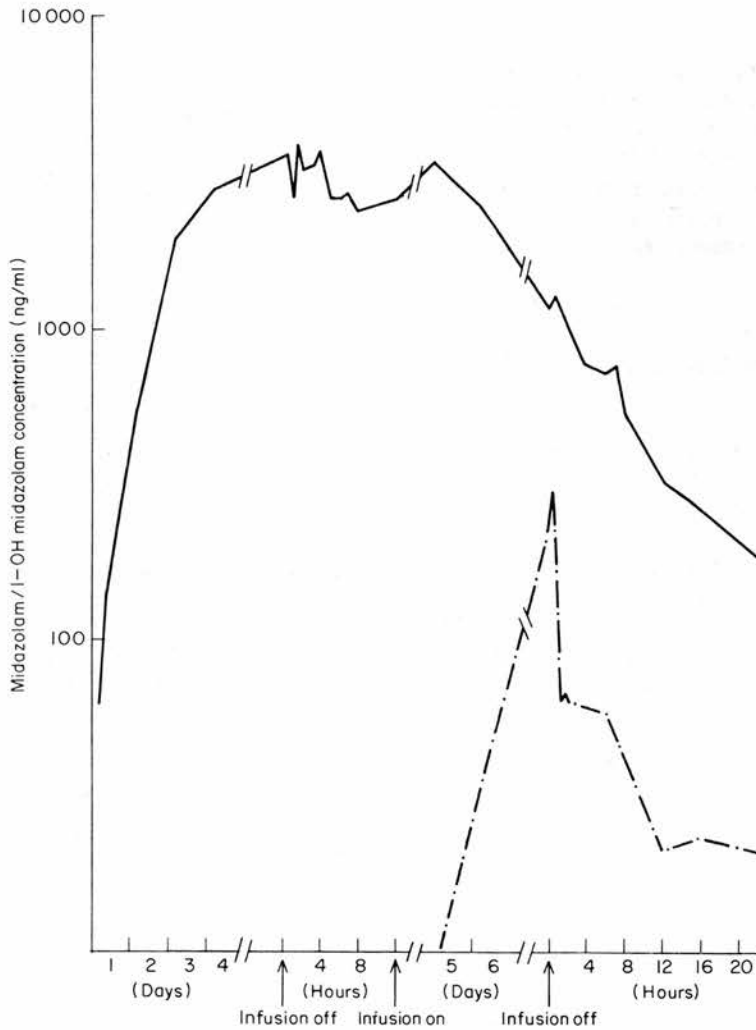


Fig. 2. Plasma midazolam and 1-OH midazolam concentrations for patient F during the study period, including both occasions the midazolam infusion was discontinued. —, Plasma midazolam concentration; - · - ·, plasma 1-OH midazolam concentration.

decreased and 1-OH midazolam increased, which indicates that clearance was returning towards normal. The plasma concentrations of midazolam and 1-OH midazolam for patient E throughout the period of his infusion are shown in Fig. 1. Plasma concentrations of midazolam increased rapidly after the start of the infusion and reached a peak on day 4. Plasma concentrations of 1-OH midazolam were low or absent during this time. On day 5, which coincided with the patient's first period of haemodialysis, the plasma concentration of midazolam decreased

but that of 1-OH midazolam increased. Following this, the plasma concentrations of midazolam and 1-OH midazolam decreased to a steady-state level which was maintained until the infusion was discontinued. The phase immediately following discontinuation was not studied in this patient but, 24 hours after cessation of the infusion, no midazolam or 1-OH midazolam were detectable in the plasma.

The plasma concentrations of midazolam and 1-OH midazolam for patient F during his entire study period are shown in Fig. 2. Plasma con-

centrations of midazolam again increased rapidly to high levels by day 4 but, following the first cessation of the infusion, the levels remained high. No 1-OH midazolam was detected in the plasma during this period. After the infusion was restarted plasma midazolam concentrations declined slightly until the infusion was finally stopped on day 8. Following this, the plasma concentration decreased to therapeutic levels within 24 hours.

Table 5 shows the time taken for the patients to wake and the plasma concentrations of midazolam and 1-OH midazolam at this time.

Table 5. Time taken for patients to wake following cessation of midazolam infusion, and plasma midazolam and 1-OH midazolam concentrations at this time.

Patient	Time to wake (hours)	Plasma midazolam concentration (ng/ml)	Plasma 1-OH midazolam concentration (ng/ml)
A	0	117	25
B	11	365	43
C	2	97	40
D	12	519	32
E	*	0	0
F a	†	2582	0
b	24	166	20

* Remained unrousable.

† Infusion restarted because of agitation.

a, First cessation, b, second cessation of midazolam infusion.

Discussion

Few drugs are currently available which will predictably produce adequate sedation in patients who receive intensive care. Midazolam has been used to induce anaesthesia¹⁸ and to produce sedation¹⁹ in healthy patients and its use has been extended to the critically ill patient in the intensive care unit. Continuous intravenous infusion of midazolam produces satisfactory sedation but prolonged awakening has been reported in some patients.⁹⁻¹¹ A considerable variation in individual response to midazolam has been reported previously; the elderly are particularly sensitive.²⁰ The prolonged sedation seen in critically ill patients following midazolam may represent part of a spectrum of response and may reflect altered hepatic blood flow⁹ or impaired metabolic capacity.²⁰ The patients reported here show three different pharmacokinetic and pharmacodynamic patterns, which

appear to be related to the severity of the patient's disease.

The two patients (A and C) with the lowest APACHE II and sepsis scores had normal pharmacokinetic parameters. In both these patients, plasma concentrations of midazolam and 1-OH midazolam decreased rapidly and both woke soon after the infusion was discontinued. At the time of awakening, plasma concentrations of midazolam were approximately 100 ng/ml and concentrations of 1-OH midazolam were approximately 30 ng/ml.

All the remaining patients had a low plasma clearance and a prolonged elimination half-life of midazolam. Two of these patients (B and D) had intermediate APACHE II and sepsis scores. The prolonged elimination of midazolam in these patients, was associated with a large volume of distribution and normal plasma concentrations of 1-OH midazolam. These patients remained sedated for approximately 12 hours after cessation of the infusion and were awake, with plasma concentrations of midazolam normally associated with sedation. Plasma concentrations of 1-OH midazolam were again approximately 30 ng/ml. Patients who undergo major surgery and patients with chronic renal failure have an altered volume of distribution of midazolam.^{20,21} This change has been attributed to reduced protein binding of the drug, which leads to a higher free drug fraction.²¹ A similar mechanism may be responsible for the large volume of distribution of midazolam in these patients, both of whom had impaired renal function. Their concentrations of serum albumin were normal but its ability to bind midazolam may have been altered by disease or other drugs administered concomitantly.²²

The remaining two patients (E and F) both initially suffered from septic shock and had high APACHE II and sepsis scores; both patients received inotropic support. These two patients initially had a reduced clearance associated with low or absent plasma concentrations of 1-OH midazolam. The plasma concentration of midazolam in these patients reached high levels (3000 ng/ml) on the 4th and 5th day of their infusions but no adverse haemodynamic or biochemical effects of these high concentrations were noted. Both patients subsequently showed clinical evidence of improvement and their APACHE II and sepsis scores decreased. This improvement was associated with the appearance

of 1-OH midazolam in their plasma and an increase in midazolam clearance towards normal. In patient E, this change coincided with his first period of haemodialysis. This did not initiate his improvement but is a reflection of it, since haemodialysis could not be undertaken in the presence of haemodynamic instability. Furthermore, similar changes in the plasma concentrations of midazolam and 1-OH midazolam were not seen when haemodialysis was repeated.

The high plasma concentrations of midazolam and the absence of metabolite suggest that impaired metabolism resulted in its cumulation. A reduction in the metabolism may result from reduced liver perfusion or an enzyme defect.²³ The increase in midazolam clearance as the patients' condition improved, however, suggests a reversible impairment rather than an inherited reduction in midazolam metabolism.²⁰ Because midazolam has a high hepatic extraction, the rate of its metabolism is dependent on hepatic blood flow and any reduction in liver perfusion could reduce the rate of its metabolism.⁹ Acute hypovolaemia in dogs lowered the clearance of midazolam, without changes in volume of distribution or in protein binding.²⁴ Midazolam itself has been shown to affect splanchnic blood flow. Following bolus administration, hepatic arterial flow decreases and portal venous flow, after an initial rise, also falls.²⁵ The haemodynamic stability that follows administration of midazolam is thought to be due to compensatory mechanisms which lead to redistribution of blood within the splanchnic bed; this may also occur in man.²⁶

Both these patients were sedated for a prolonged period following cessation of the infusion. Patient E remained unrousable until his death, in spite of undetectable plasma concentrations of midazolam and 1-OH midazolam 22 hours following the infusion; this may have been due to the prolonged effect of other drugs or to his severe illness. After the midazolam infusion of patient F had been discontinued, it was restarted because of agitation which occurred in spite of a high plasma concentration. However, when the infusion was discontinued for a second time, he woke with a plasma concentration of midazolam within the sedative range and a plasma 1-OH midazolam concentration of 20 ng/ml. Overall, there appeared to be no correlation between plasma midazolam concentration and the time at which the patient woke following the infusion.

There does, however, appear to be an association between waking and the plasma concentration of 1-OH midazolam; patients awoke with levels between 20 and 40 ng/ml.

Plasma concentrations of 1-OH midazolam are lower than those of the parent drug and this represents a wide range. However, it may be that the action of midazolam is influenced by its metabolites in the same way as the effects of morphine appear to depend upon its metabolites.^{27,28}

Acknowledgments

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Early metabolic changes after liver operations

Jean Pierre Lançon, Michael Lindop, Gilbert Park and John Farman

Introduction

Patients who have had major operations, such as portal-systemic venous shunts for cirrhosis, entero-hepatic anastomoses for biliary obstruction, operations for liver trauma or liver transplantation are usually admitted to the ICU for postoperative care. In our hospital they are initially ventilated artificially for some hours, until blood loss has been controlled, analgesia established by appropriate means and consciousness (which may have been impaired by encephalopathy) has been recovered.

The ICU stay may be divided into two phases. The initial phase, covering the first hours following the procedure, is a period of stabilisation with effectively a continuation of the intra-operative management, with close cardiovascular and biochemical monitoring. The second phase is a period of recovery, dominated by the need for pain relief and resumption of respiratory function, and characterised by important metabolic changes associated with the return of liver function, in a patient who may previously have been in end-stage liver failure. The postoperative period is also marked by the late effects of the massive blood replacement which is sometimes needed in patients with coagulopathy due to liver failure.¹ All are factors which can influence renal, hepatic and other organ functions.

In this review metabolic and other changes encountered during the early days following one such operation, liver transplantation, when the patient requires intensive care, are described.

Patients and methods

This paper reviews the postoperative courses of 38 patients who underwent liver transplantation as described by Calne² at Addenbrooke's Hospital in Cambridge.

Dr Lançon is from the Centre Hospitalier Régional and University of Dijon. Dr Lindop, Dr Park and Dr Farman work in the ICU at Addenbrooke's Hospital, Cambridge, where these observations were made.

All of them were assessed preoperatively according to a standard protocol.³

The preoperative diagnoses are shown in Table 1. Their distribution is representative of the entire range of conditions likely to lead to ICU admission, with the exception of acute hepatic failure. Preoperative investigations are shown in Table 2. The liver score,⁴ attesting the severity of liver dysfunction and hence of operative risk, was calculated.

The anaesthetic and the perioperative management was as previously described;³ during the procedure, 20 patients received isoflurane in concentrations up to 1.5 per cent while 18 received up to 0.5 per cent

trichloroethylene. The addition of nitrous oxide to oxygen depended on the choice of the anaesthetist. Fentanyl was employed as required for analgesia and maintenance relaxation was provided with atracurium or vecuronium, either as boluses or as an infusion, or with bolus pancuronium.

At the end of the operation, the patients were transferred to the intensive care unit. Weaning from the ventilator was usually achieved within the first 24 hours, depending on haemodynamic stability, satisfactory pulmonary function and the absence of any important abdominal bleeding. Children weighing 10 kg or less were usually artificially ventilated for a period of 2 days. During this phase, analgesia was provided with intravenous bolus doses of either morphine or fentanyl.⁵ As the patient is being weaned from the ventilator, bilateral intercostal blocks are performed for the relief of parietal pain,⁶ the remaining visceral pain being treated with as-required intravenous bolus opioids. Sedation and anxiolysis were provided by intermittent doses of midazolam. The duration of artificial ventilation and the need for intravenous analgesia and sedation were recorded.

Monitoring of hepatic, renal and hemopoietic function followed the pattern shown in Table 3. Haemoglobin concentration was recorded as part of the blood count, although this did not reflect changes in body production of red cells so much as the use of blood transfusion or venesection. Other results, such as urine output or arterial blood gases, although monitored throughout the ICU stay, are

Table 1. Diagnoses, number of deaths and lengths of stay (LOS mean \pm SD) in the ICU in the 38 patients.

Diagnosis	No	%	Deaths	LOS (days)
Primary biliary cirrhosis	9	24	2	3.5 \pm 1
Metabolic disease	6*	16	1	4.3 \pm 2.5
Sclerosing cholangitis	5	13	2	9.5 \pm 7.8
Liver tumour	4	11	1	2.7 \pm 0.5
Chronic active hepatitis	3	8	0	5.7 \pm 3.3
Retransplantation	3**	8	1	7.5 \pm 1.5
Cryptogenetic cirrhosis	2	5	0	5.5 \pm 2.5
Alcoholic cirrhosis	2	5	0	4.0 \pm 1
Polycystic disease	2	5	0	7.0 \pm 2
Others	2***			

*Wilson's disease 2, antitrypsin deficiency 2, Crigler-Najjar's disease 1, tyrosinosis 1.

Acute rejection 2, (48 h 20 days), chronic rejection 1. *Biliary atresia 1, Budd-Chiari syndrome 1.

Table 2. Patient's preoperative details (mean \pm SD (range))

	Mean	SD	Range
Age (years)	35	16	(3-55)
Liver score	9.3	2.7	(5-14)
Haemoglobin (mg/100 ml)	11.3	1.8	(6-15)
White cells ($\times 1000$ /ml)	8.8	4.7	(3-19)
Platelets ($\times 1000$ /ml)	232	175	(45-748)
Albumin (g/l)	26	8	(12-46)
Bilirubin (μ mol/l)	272	274	(7-1204)
Alkaline phosphatase (U/l)	624	90	(13-3644)
ALT (U/l)	154	273	(4-1668)
Urea (mmol/l)	9.2	13.3	(1-75)
Creatinine (μ mol/l)	128	134	(15-760)

Table 3. Monitoring of hepatic, renal and haemopoietic functions following liver transplantation

	Electrolytes*	LFT**	Blood count
On arrival	+		+
6 h	+		+
12 h	+	+	+
24 h	+	+	+
Daily	+	+	+

*Sodium, potassium, urea, creatinine, glucose.

**LFT, liver function tests: total proteins, albumin, phosphatase, bilirubin, alkaline phosphate, alanine amino transferase.

believed to reflect mainly the quality of care and so are not reported here. If the patient was exposed to nitrous oxide, hydroxycobalamin and folic acid were given for the first two postoperative days to reduce the bone marrow toxicity which follows the employment of this agent for long procedures.⁷

Results

The patients' ages ranged from 3 to 55 years (mean 35, SD 16 years), with liver scores between 5 and 14 (mean 9.3), indicating a moderate level of risk. Of the 38 patients, 7 died during their stay in the ICU (6 during the first week), 5 from major intra-abdominal bleeding, 1 from viral infection and 1 from multi-organ failure. The mean duration of stay in the ICU was 7 days (SD 9 days); seven patients stayed more than one week. The duration of artificial ventilation was 37 (SD 30) hours, intravenous analgesia was needed for 67 (SD 51) hours, and sedation for 42 (SD 36) hours.

Over the first postoperative week, albumin concentrations were almost constant, with values a little higher in the 12 and 24 hour samples compared with the preoperative levels, although always remaining below the normal range, as shown in Figure 1.

Following a reduction in the first 24 hours, the bilirubin concentration remained constant until the third day and then started to increase, reaching a value near the preoperative level by the 7th day. This is shown in Figure 2.

After operation there was a striking decrease over the first two days in alkaline phosphatase values, which then remained almost constant for the remainder of the week (Fig. 3).

By contrast the ALT (Alanine aminotransferase) increased during the first day, reaching a level 5 times greater than the preoperative value, as shown in Figure 4, and then decreased over the next two days, thereafter remaining constant.

Despite a transient increase followed by a reduction over the first 24 hours, urea levels tended to increase slightly from the preoperative values (Fig. 5).

Creatinine levels increased during the first day following surgery and then fell again, to reach their preoperative values on the 3rd day although remaining slightly above normal (Fig. 6).

The platelet count, shown in Figure 7, fell until the third day and then rose again up to the end of the second week.

The white cell count remained unchanged for the first 3 days, and then started to increase, reaching a mean value of 17 200/ml at the end of the second postoperative week (Fig. 8).

Discussion

Albumin infusions are given throughout the early postoperative period to compensate for losses from the wound via the drains, so serum levels reflect mainly the effectiveness of replacement therapy. During the course of this period the loss via the drains decreased, while at the same time the liver presumably resumed

Figure 1. Changes in serum albumin in the first week after operation.

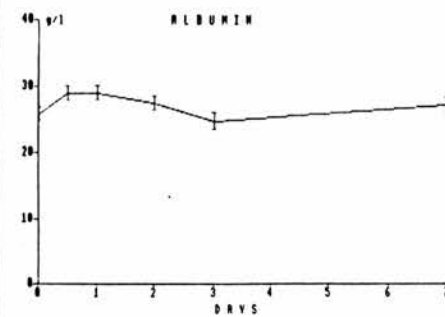


Figure 2. Serum bilirubin levels in the postoperative period.

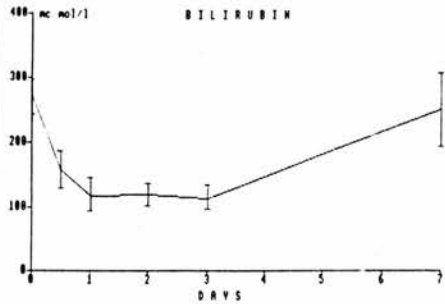


Figure 3. Evolution of the serum alkaline phosphatase after major liver surgery.

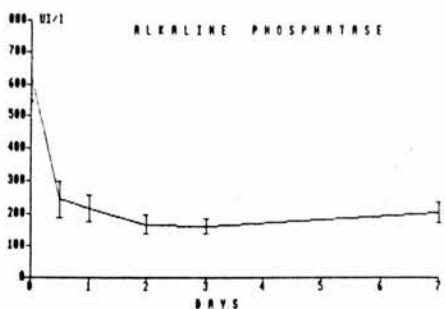


Figure 4. ALT levels rise on the first postoperative day, and then decay gradually.

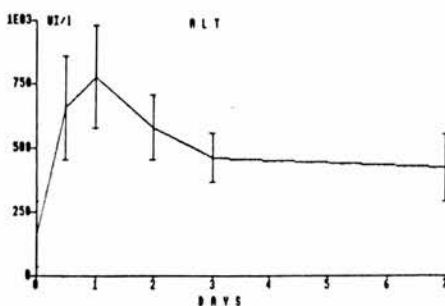


Figure 5. Changes in blood urea after operation; the increase over the first few days is due to part to greater production by the liver.

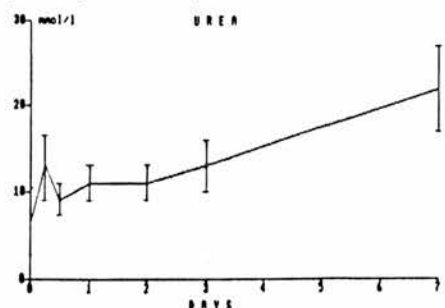


Figure 6. Serum creatinine levels rise at first, presumably reflecting tissue destruction, and then return to the control level. Note the wide Standard Deviation.

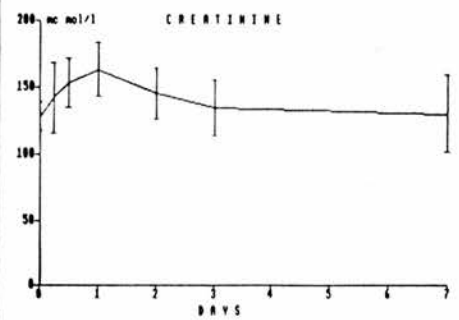


Figure 7. The platelet count falls at first, then recovers, reaching normal levels within two weeks.

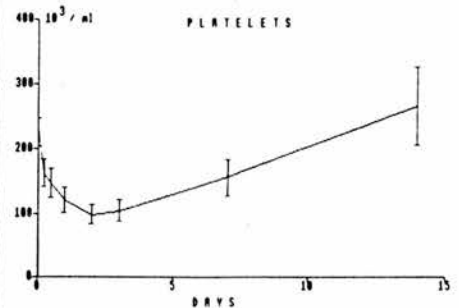
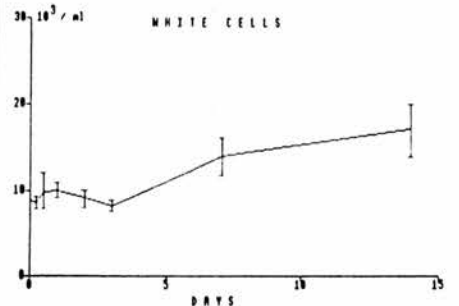


Figure 8. The white blood count rises after the first three days following liver transplantation; this may reflect immune suppression.



production of albumin, explaining the slight increment observed at the end of the first week.

The trend of bilirubin levels may be divided into 3 parts; the first immediately follows transplantation, when the elimination of the excess bilirubin occurs, the second is a plateau representing a balance between production and elimination and the third, beginning on the third day, is when production exceeds the rate of elimination, possibly as a consequence of haemolysis associated with massive blood transfusion. Moreover, this occurs during the period that often sees the first episode of rejection of the transplanted liver (commonly from 5 to 14 days after surgery).⁸

Changes in alkaline phosphatase levels demonstrate the metabolic activity of the liver. The steep slope of the first part of the curve is explained by the catabolism of this enzyme, which normally has a half-life of around 40 hours. The slight increase

Table 4. Mean values (\pm SD) of the variables studied over the course of the first week in 38 patients

	6 h	12 h	24 h	48 h	72 h	Day 7
Albumin (g/l)		28.8 (4.2)	29 (4.5)	27.5 (5.4)	24.7 (5.5)	26.5 (5.3)
Bilirubin (μ mol/l)		157 (121)	117 (114)	118 (80)	114 (81)	250 (230)
Alk. phosphatase (U/l)	244	216 (238)	166 (192)	160 (132)	204 (106)	(127)
ALT (U/l)		658 (919)	778 (990)	579 (644)	461 (453)	425 (533)
Urea (mmol/l)	13 (24)	8.8 (6.2)	11 (12)	11.3 (13)	12.9 (13.5)	22 (22)
Creatinine (μ mol/l)	142 (106)	153 (91)	163 (110)	146 (97)	135 (100)	130 (117)
White cells ($\times 1000$ /ml)	8.5 (4)	10 (5.5)	10.2 (4.2)	9.2 (4.6)	8.2 (8.2)	14.4 (14.4)
Platelets ($\times 1000$ /ml)	162 (114)	146 (118)	120 (105)	98 (79)	104 (86)	157 (125)
Haemoglobin (mg/100 ml)	12.8 (2.6)	12.9 (3)	12.7 (2.6)	12.8 (2.3)	12.5 (2.1)	13.1 (1.9)

observed at the end of the first week may also be related to episodes of rejection during this period, although there is a dissociation between the marked increase in bilirubin and the relative stability of the alkaline phosphatase. In the case of transplantation the liver has to recuperate from a long cold ischaemic period of preservation, inevitably associated with a degree of cytolysis, reflected by the increase in ALT levels during the first postoperative day. Regeneration of destroyed hepatocytes seems to begin within 24 hours of surgery, although on the 7th postoperative day blood levels are still greater than preoperative values, which may be due to episodes of rejection.

Renal function is also affected by major liver operations, but plasma urea and creatinine levels depend on hepatic as well as renal function; the slight increment in these levels seen at the end of the operation is a consequence of the haemodynamic perturbation associated with such procedures. Thereafter the rising urea level may be an expression of increasing production by the liver. The dopamine infusion, given to protect renal function during and after surgery, is usually stopped on the second day after surgery, which may contribute to the increase in blood levels by reducing urea clearance. Changes in creatinine levels do not parallel those of urea; here again the rising part of the curve, from the end of the operation to the end of the first postoperative day, is possibly explained by the tissue destruction occurring during the procedure. This rise is transient, the levels returning to their preoperative values within 2 days. Cyclosporin, usually introduced on the 3rd postoperative day, seems to have no major effect on plasma creatinine levels.

Platelet levels are also affected by the operation, massive blood transfusion inducing thrombocytopenia.⁹ The presence of the large wound and internal raw areas will account for a considerable consumption, which explains the reduction in the count seen at the end of the procedure. The first hours following the operation may be marked by persistent

intra-abdominal bleeding, necessitating the continuation of transfusion. No platelet transfusion is given as long as the count does not fall below 50 000/ml, unless bleeding continues, so the mean trend is downwards. When the bleeding ceases the platelet count increases, reaching normal levels some two weeks later. Numerous factors affect the white cell count, including rejection and infection, which may be an explanation for the tendency of the curve to rise.

In conclusion, the results describe the recovery of liver function in a series of typical patients after major liver operations. It is clear that the changes described are affected by many factors which depend both on the patients and on their preoperative diagnoses. Nevertheless they represent a good model for all patients receiving intensive care following major hepatic operations.

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Forum

Intercostal nerve blockade for children

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Summary

A modified technique of intercostal nerve blockade is described which is suitable for use in children. Ten patients received intercostal nerve blockade on a total of 29 occasions in order to provide analgesia following liver transplantation and to facilitate weaning from artificial ventilation of the lungs. The opioid requirement of patients who received intercostal nerve blockade was considerably lower than that of those who did not; 56% of the children who received intercostal nerve blockade required no additional analgesia. One child, the first to receive intercostal nerve blockade, developed a pneumothorax following the procedure. The technique has proved to be safe in skilled hands. It is an acceptable method of postoperative analgesia in children after liver transplantation and may be a useful technique in the management of other paediatric patients.

Key words

*Anaesthetic techniques, regional; intercostal.
Anaesthesia; paediatric.*

Interest in nerve and regional blockade for children has been slow to develop. Penile nerve block or caudal analgesia are often used to supplement anaesthesia and provide postoperative analgesia for operations such as circumcision, but other techniques are employed less frequently. Local analgesic blocks in children have a number of problems, particularly for the occasional paediatric anaesthetist.¹ These include the practical difficulties of dealing with small children, their variations from the more familiar adult anatomy, the different equipment or techniques that may be appropriate and the lack of information regarding the pharmacokinetics of local anaesthetics in paediatric patients. The mobility and distress produced by repeated injections in the awake child are a further complication.

Intercostal nerve blockade is used widely in adults, both intra-operatively and for postoperative analgesia;² it has also been suggested as suitable for the same indications in children.³ The risk of pneumothorax is the main disadvantage of intercostal nerve blockade but its reported incidence in adults varies

widely² and appears to be operator dependent; no incidence has been quoted in children.

Intercostal nerve blockade is performed following liver transplantation in adults, to aid weaning from artificial ventilation of the lungs. Provision of adequate analgesia is difficult in this group of patients since the surgical incision is large: a bilateral subcostal incision with an upward extension to the xiphisternum. Analgesia is required both to allow effective physiotherapy and to reduce the high incidence of respiratory complications following liver transplantation. Opioid analgesics produce sedation and are antitussive. In addition, the elimination of morphine appears to be abnormal in patients following liver transplantation⁴ and this may be further exacerbated by impaired renal function.⁵

We have evolved a modification of a standard method for intercostal nerve blockade in order to provide postoperative analgesia for children following liver transplantation. The technique may also benefit other children who require thoracic or abdominal surgery.

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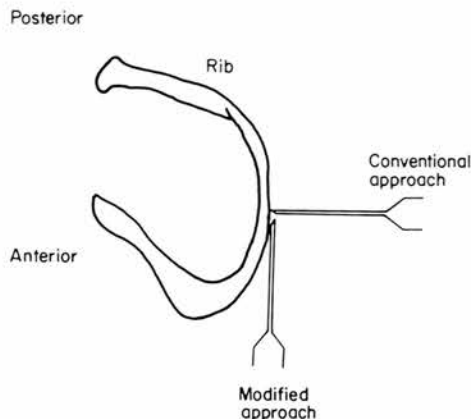


Fig. 1. Position of the needle relative to the rib when intercostal nerve blockade is performed by the conventional and the modified technique.

Methods

Technique of intercostal nerve blockade. The technique of intercostal nerve blockade is a modification of that described for adults in the mid-axillary line.⁶ The local analgesic used is bupivacaine without adrenaline; 2 mg/kg are diluted to give a volume of 1 ml for each intercostal space to be blocked. In the smaller child 0.25% bupivacaine is diluted, if necessary, with 0.9% saline to give a final concentration of approximately 0.125%, and in larger children 0.5% bupivacaine is diluted to give an approximate concentration of 0.375%. A 100-cm length of low-deadspace manometer tubing is primed with the solution so that a remote needle technique can be used with a second operator to inject the solution.⁷

The patient is placed in either the lateral or supine position and restrained firmly. The skin is cleaned and the rib palpated in the mid-axillary line. A 25-gauge needle is introduced perpendicularly through the skin onto the rib and gently walked down the rib to its caudad edge. At this point, the needle is angled posteriorly and advanced slightly medially and posteriorly so that it is almost parallel to the rib, until the tip of the needle lies 1–2 mm beneath the edge of the rib. The bevel of the needle faces cephalad (Fig. 1). A loss of resistance is frequently experienced and the needle felt to slide into the subcostal space. The assistant who holds the syringe is asked to aspirate while the needle is held firmly in position, with the back of the right hand supported against the patient and the left hand palpating the rib or steadying the needle (Fig. 2). If no blood or air is withdrawn, 1 ml of solution is injected and the needle removed. It is necessary to block the intercostal nerves bilaterally at T₆–T₁₁ inclusive following liver transplantation.

Patients. Twenty children under the age of 10 have undergone liver transplantation at this centre to date.



Fig. 2. Position of the hands and needle during intercostal nerve blockade in children using the modified technique.

Intercostal nerve blockade was performed in the immediate postoperative period to facilitate weaning from controlled ventilation. Not all of the children received nerve blocks during this period, either because of the absence of an operator familiar with the technique or because of a continuing need for controlled ventilation. Local analgesia was routinely supplemented by bolus opioid administration as necessary to relieve visceral pain.

The records of all 20 patients were reviewed to assess the efficacy of intercostal nerve blockade in this group and the incidence of any complications. To assess analgesic efficacy, opioid requirements on the third postoperative day were converted to morphine equivalents⁸ and expressed as mg morphine/kg for that day. Intercostal nerve blocks were performed in the intensive care unit during the first 4 days postoperatively. However, the third postoperative day was chosen to assess analgesic requirements because weaning from artificial ventilation had generally been achieved by this time and pain from the surgical incision was still sufficiently severe to impair respiration as well as to cause distress. At least one erect chest X ray was taken daily in these children, to enable prompt and accurate identification of any pneumothorax.

Results

The 20 children had a total of 21 operations: one patient underwent retransplantation in the early postoperative period. Ten of the children received intercostal nerve blockade on a total of 29 occasions after 11 operations. Ten intercostal nerves were blocked on each occasion. The other ten children did not receive nerve blocks; analgesia was provided in these cases by intravenous opioids.

Analgesic requirements on the third postoperative day were not determined for seven cases. Two cases received intercostal nerve blockade as part of their postoperative analgesic regimen but this was omitted on the third postoperative day because no skilled operator was available. The other five patients did not receive intercostal nerve blockade; two had died by the third postoperative day and information for the other three was incomplete and analgesic requirements could not be assessed for that day. The details of the 14 patients whose analgesic requirements were reviewed, are shown in Table 1. Nine of the patients

Table 1. Details of patients.

	Intercostal block (n = 9)	No block (n = 5)
Mean age, years (range)	3.7 (1.1–7.0)	2.8 (2.0–3.5)
Sex, M:F	4:5	2:3
Mean weight, kg (range)	14.2 (10–22)	12.8 (8–22)
Diagnosis		
Biliary atresia	6	3
Neonatal hepatitis	1	1
Alpha-1-antitrypsin deficiency	1	—
Drug-induced	1	—
Angiocarcinoma	—	1

received intercostal nerve blockade and their tracheas were extubated on or before the third postoperative day. Of the five patients who did not receive intercostal nerve blockade, two were extubated on the third postoperative day; the other three received controlled ventilation.

The nine patients who received intercostal nerve blockade required a mean dose of 0.16 mg/kg morphine (SD 0.27) on the third postoperative day; the corresponding dose in those who did not receive the nerve block was 1.52 mg/kg (SD 0.93). All patients who did not receive a nerve block, required opioid.

The three patients who still required controlled ventilation on the third postoperative day had more severe illness and were sedated with midazolam in addition to morphine. They received a mean of 1.04 mg/kg morphine on that day; the two patients whose tracheas were extubated on the third postoperative day, however, received a mean of 2.25 mg/kg morphine on that day. Most of the children received intercostal nerve blockade on two or three occasions during and after weaning from artificial ventilation. The duration of analgesia on each occasion was approximately 12 hours.

The complication rate of the technique was low. Two of the 20 children developed a unilateral pneumothorax, but one child had not received intercostal nerve blockade, while the other had received intercostal nerve blockade 3 days previously and was the first patient on whom the technique was performed. The children frequently slept after administration of the blocks; none had evidence of systemic local anaesthetic toxicity. Two patients developed sputum retention after early discharge from the intensive care unit. Both received intercostal nerve blockade initially but were subsequently given relatively high doses of morphine for analgesia and sedation on the ward.

Discussion

Children who undergo liver transplantation are a small but uniform group. Few other abdominal procedures are performed in children, that require the same degree of effective analgesia to relieve severe postoperative pain over a prolonged period. Intercostal nerve blockade is an established and effective technique for intraoperative and postoperative analgesia in adults.² Use of the technique has been shown to reduce postoperative opioid requirements and respiratory impairment.³ The main disadvantage is the incidence of pneumothorax and, in children, the smaller anatomical distances involved may increase this risk. A mid-axillary approach is used in the technique described above to reduce the likelihood of pneumothorax.⁹ The risk of pleural puncture is further decreased because the needle enters the intercostal space at an acute angle, almost parallel to the rib. Thoracic epidural analgesia is not employed in these patients because of the bleeding disorders frequently encountered in patients with liver disease, and the risk of hypotension due to sympathetic nerve blockade.

Intercostal nerve blockade has a number of advantages over opioid analgesia following liver transplantation. A large surgical incision is present and adequate analgesia without profound sedation may be difficult to achieve with opioids. Postoperative respiratory complications are common in patients following liver transplantation, and good pain relief with a cooperative patient and without respiratory depression is essential for effective physiotherapy. The importance of these points is illustrated by the two children who developed sputum retention due to sedation following opioid analgesia. A postoperative ileus invariably develops after liver transplantation and recovery of effective gastrointestinal motility is hastened if the opioid dose can be reduced. The antidiuretic effect of morphine may further impair already compromised renal function in these patients. Adequate renal function is important in the elimination of morphine² and, if impaired, may exacerbate the abnormal elimination pattern already present in these patients.⁴ Opioid-induced nausea and peripheral vasodilatation may also

cause problems which can be avoided by intercostal nerve blockade. This study reports only a small number of patients but the use of intercostal nerve blockade immediately prior to weaning from artificial ventilation, and repeated as necessary afterwards, reduced opioid requirements significantly during this period.

The complications of intercostal nerve blockade include pneumothorax, haematoma formation and local anaesthetic toxicity from inadvertent intravascular injection. One child who received intercostal nerve blockade suffered a small unilateral pneumothorax but that occurred 3 days after his last intercostal blockade. Since he was the first patient to receive a block, this may reflect lack of experience of the technique; no subsequent patient developed this complication. Pneumothorax is a complication of artificial ventilation itself, particularly in children, and one other child who did not receive an intercostal block, also suffered a unilateral pneumothorax. The pneumothorax in this patient was associated with barotrauma during controlled ventilation of noncompliant lungs following the development of respiratory distress syndrome after inadvertent administration of cyclosporin into a central vein.¹⁰

All patients had slightly impaired clotting indices at the time of the blocks but neither bleeding nor haematoma formation proved a problem. Systemic local anaesthetic toxicity was not observed, although a maximum bupivacaine dose of 4 mg/kg has been recommended,¹¹ but a dose of 2 mg/kg was administered to these patients because of their impaired liver function. Sleep following intercostal nerve blockade was a consistent feature. This may be due to several factors: sedation is a side effect of local anaesthetic agents and may be particularly apparent when relatively large doses are used or when rapid uptake occurs; satisfactory analgesia may cause a tired child to sleep; and, finally, the performance of the blocks or subsequent physiotherapy may themselves tire the child. Although sleepy, the children were always rousable and cooperative. No other complications of the procedure have been noted and the children appeared to forget quickly the temporary discomfort of the repeated injections.

The modified technique of intercostal nerve blockade described, has been found to provide effective postoperative analgesia with a reduction in opioid requirements.

Acknowledgments

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HAEMODYNAMIC EFFECTS FOLLOWING SURGICAL RELEASE OF INCREASED INTRA-ABDOMINAL PRESSURE

M. P. SHELLY, A. A. ROBINSON, J. W. HESFORD AND G. R. PARK

Although the haemodynamic effects of increased intra-abdominal pressure have been documented, the changes which immediately follow decompression have not. We report the haemodynamic changes observed on four occasions immediately before and after the release of abdominal tamponade resulting from intra-abdominal bleeding. Measurements made during the release of the tamponade in the first patient indicated that rapid blood transfusion at the time of decompression was inappropriate. Observations were, therefore, made in a more controlled manner in two further patients on three subsequent occasions, when more personnel were available to assist with the more frequent and intensive monitoring of cardiovascular function.

CASE REPORTS

Patient 1

The first patient was a 35-year-old man who underwent orthotopic liver transplantation for hepatic failure secondary to sclerosing cholangitis. After surgery he continued to bleed from intra-abdominal sites and required massive blood transfusion; blood was lost from abdominal drains and he developed a tense distended abdomen. His coagulation screen was slightly abnormal in spite of the infusion of fresh frozen plasma and platelet concentrate, but there was no clinical evidence of a significant coagulation disorder—such as bleeding from the nose, mouth, pharynx or the sites of venous and arterial cannulation.

Eight hours after his liver transplant operation, laparotomy was undertaken to evacuate intra-

SUMMARY

The haemodynamic indices of three patients, who developed abdominal tamponade as a result of intra-abdominal bleeding following liver transplantation, were measured on four occasions as the increased intra-abdominal pressure was released. Hypotension followed the release of the tamponade in all patients and was the result of a decrease in systemic vascular resistance. This was treated with vasoconstrictors; the response to various agents was monitored. Treatment of hypotension following release of abdominal tamponade by volume replacement alone may be inappropriate and may lead to over-transfusion; adrenaline may be the treatment of choice. Intensive haemodynamic monitoring is advisable.

abdominal clot and to achieve haemostasis. During the re-exploration, cardiovascular variables were measured: heart rate (HR) was taken from the electrocardiogram, mean arterial pressure (MAP) was measured via an indwelling radial artery catheter and mean right atrial pressure (RAP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were measured using a pulmonary artery catheter (Edwards Laboratories) positioned immediately before surgery. Cardiac output (CO) was measured by a thermodilution technique and values were calculated for systemic (SVR) and pulmonary (PVR) vascular resistances.

On opening the peritoneal cavity, approximately 6 litre of blood and clot was removed. No arterial bleeding points were found to account for the haemorrhage; there was a general ooze from many intra-abdominal sites. Intraoperative hypotension was treated with blood transfusion; however, since calculation showed the SVR to be

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patient on two occasions (3a and 3b). Morphine and midazolam, administered for analgesia and sedation on the Intensive Care Unit were continued up to the time of surgery at a dose of 3–5 mg h⁻¹ for each agent. A period of stabilization was allowed after the induction of anaesthesia (with fentanyl 50 µg and ketamine 100 mg). No neuromuscular blocking agents were administered. On account of the results of the intensive intraoperative monitoring of the first patient, these patients were monitored using the same techniques and rapid blood transfusion was withheld. Peak airway pressures were also noted and arterial blood was sampled at intervals for

estimation of oxygen and carbon dioxide tensions, and electrolyte concentrations. In one patient, end-tidal carbon dioxide concentration (E'_{CO_2}) was monitored, together with core and peripheral temperatures using temperature probes in the nasopharynx and on the foot. Haemodynamic measurements were made frequently throughout the perioperative period.

The haemodynamic measurements made before and after the decompression in patients 2 and 3 are shown in table II. Heart rate decreased on all occasions, as did mean arterial pressure; there was an increase in CO and a sharp decrease in SVR. Patient 3, during his first laparotomy (3a), was able

TABLE II. Haemodynamic changes seen before, and after, decompression of abdominal tamponade in patients 2 and 3. HR = Heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; RAP = right atrial pressure (mean); PCWP = pulmonary capillary wedge pressure; CO = cardiac output; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; CT = core temperature; PT = peripheral temperature; E'_{CO_2} = end tidal carbon dioxide concentration

	Patient	Before decompression	After decompression
HR			
(beat min ⁻¹)	2	120	107
	3a	120	110
	3b	111	109
MAP			
(mm Hg)	2	76	35
	3a	69	67
	3b	59	38
MPAP			
(mm Hg)	2	31	15
	3a	25	25
	3b	36	19
RAP			
(mm Hg)	2	23	12
	3a	14	17
	3b	20	10
PCWP			
(mm Hg)	2	32	18
	3a	19	17
	3b	22	10
CO			
(litre min ⁻¹)	2	3.6	4.9
	3a	7.4	10.2
	3b	10.3	12.2
SVR			
(dyn s cm ⁻⁵)	2	1177	376
	3a	594	392
	3b	302	183
PVR			
(dyn s cm ⁻⁵)	2	160	93
	3a	65	63
	3b	108	59
CT (°C)	3b	37.0	36.7
PT (°C)	3b	28.8	30.7
E'_{CO_2} (mm)	3b	5.6	7.2

TABLE III. Changes in some of the cardiovascular variables following intra-operative administration of various sympathomimetic agents in patients 2 and 3. HR = Heart rate; MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance. b = Bolus; i = infusion; * not noted

	Patient	Before methox-amine	After methox-amine	Before ephed-rine	After ephed-rine	Before vaso-pressin	After vaso-pressin	Before adren-aline	After adren-aline
Dose	2					10 u.		b 0.3 mg i 4.0 mg h ⁻¹	
	3a	10 mg		15 mg					
	3b	20 mg				7 u. 10 u.		b 0.3 mg i *	
HR (beat min ⁻¹)	2					107	120	b 120 i 127	b 127 i 137
	3a	109	111	109	133				
	3b	102	100			126 111	115 101	b 100 i 110	b 82 i 111
MAP (mm Hg)	2					35	44	b 44 i 53	b 53 i 57
	3a	56	58	48	60				
	3b	44	51			65 45	87 67	b 51 i 48	b 107 i 74
CO (litre min ⁻¹)	2					4.9	3.9	b 3.9 i 4.1	b 4.1 i 2.5
	3a	9.7	11.7	11.4	13.6				
	3b	10.3	9.9			12.9 10.6	11.3 9.7	b 9.9 i 10.9	b 10.0 i 12.9
SVR (dyn s cm ⁻⁵)	2					376	533	b 533 i 839	b 839 i 1560
	3a	338	267	231	282				
	3b	264	307			285 294	446 395	b 307 i 300	b 728 i 378

to maintain cardiovascular stability better than on the subsequent occasion; MAP was maintained by a considerable increase in CO. During decompression, core temperature decreased slightly while the temperature on the foot increased by 2 °C. There were marked increases in hydrogen ion concentration, P_{aCO_2} and E'_{CO_2} , and a smaller increase in potassium concentration. There was no consistent change in P_{aO_2} or in ionized calcium or sodium concentrations.

The responses of HR, MAP, CO and SVR of patients 2 and 3 to different sympathomimetic agents are shown in table III. Methoxamine had no effect on MAP, CO or SVR. However, ephedrine increased MAP slightly by increasing CO. Vasopressin increased MAP to a greater extent and in a more appropriate way by increasing SVR, but a greater increase in SVR was seen with the bolus administration of adrenaline.

There was no evidence of an additive effect between the various agents administered.

DISCUSSION

The immediate haemodynamic changes seen following the release of increased intra-abdominal pressure have not been described previously. Richards and colleagues (1983) described the haemodynamic changes in three patients before, and after, the release of abdominal tamponade—but over a longer time course and not during the operation. They observed decreases in mean arterial pressure, central venous pressure and pulmonary capillary wedge pressure after decompression, but little alteration in cardiac output or total peripheral resistance. Other studies on increased intra-abdominal pressure have been in patients undergoing laparoscopy (Kelman et al.,

1972; Lewis et al., 1972). These have produced less comprehensive, and conflicting, results which appear to be dependent on the intra-abdominal pressure (Motew et al., 1973).

Studies in dogs have described the changes seen with increasing intra-abdominal pressure (Richardson and Trinkle, 1976; Toomasian, 1978; Kashtan et al., 1981): cardiac output decreased and total peripheral resistance increased with increasing intra-abdominal pressure. This effect was most marked in dogs rendered hypovolaemic. The reduction in cardiac output was thought to reflect not only an increased peripheral resistance, but also myocardial depression and a decrease in venous return. Alterations in pleural pressure with increased intra-abdominal pressure were insignificant and thought not to contribute to the haemodynamic changes.

The variability in cardiovascular indices observed in man may be the result of different degrees of arterial compression, of cardiovascular instability at the time, and of the concurrent treatment of this instability. The latter factors were minimized as far as possible while these patients were studied. Although intra-abdominal pressure was not measured, these patients appear to have had arterial compression as well as venous occlusion in the splanchnic and lower limb vessels. The increases in temperature at the foot, and in P_{aCO_2} , E'_{CO_2} and hydrogen ion and potassium concentrations on decompression are evidence of re-established distal circulation following arterial compression. The increase in E'_{CO_2} has been noted previously in similar patients (J. V. Farman, personal communication).

Before abdominal decompression, MAP was maintained by blood transfusion; all patients had a tachycardia and RAP and PCWP were increased. Patients 1 and 2 had a reduced CO and normal SVR, but patient 3 had an increased CO, with a low SVR. All three patients had a low PVR but high MPAP.

Following abdominal decompression, there was an immediate increase in CO which was associated with a decrease in heart rate and an increase in stroke volume. There was a sharp decrease in SVR. Since the increase in CO was smaller than the decrease in SVR, MAP decreased, and since the main cause of the hypotension was a low SVR, vasoconstrictors were the most appropriate form of treatment.

Sympathomimetic agents were relatively ineffective in increasing SVR. Methoxamine had no

effect and ephedrine, although it increased MAP, did so by increasing CO, SVR remaining low. Vasopressin is an endogenous vasoconstrictor with an important action on the splanchnic vascular bed. In these patients, it caused an increase in MAP by increasing SVR. Adrenaline, which also causes splanchnic vasoconstriction, increased MAP by increasing SVR when given by bolus administration. When given by infusion, adrenaline again increased SVR, and in patient 2 this was sufficient to decrease CO so that MAP did not increase. Vascular pooling may also occur as a result of vasodilatation of the splanchnic circulation and loss of tone of the intestinal smooth muscles—the latter occurring because of hypoxia resulting from the increased intra-abdominal pressure in these patients. The action of adrenaline is complex and may depend upon smooth muscle tone (Weiner, 1985). Intensive monitoring is, therefore, advisable during its administration, particularly in this situation.

The haemodynamic changes described following abdominal decompression are compatible with the release of a high intra-abdominal pressure and the re-establishment of splanchnic and lower limb circulation. The splanchnic venous system is known to be an important blood reservoir (Greenaway, 1983) and maximal dilatation of these vessels would produce a system with a large capacity. Constriction of the splanchnic vasculature is mediated by alpha-adrenoceptors (Corday and Williams, 1960; Hirsch and Rone, 1982). These patients, however, responded poorly to sympathomimetic agents and required large doses of endogenous vasoconstrictors with a specific effect on the splanchnic circulation. This may be because of the presence of an abnormal circulation with maximally dilated vessels unresponsive to normal doses of sympathomimetic agents. This, in turn, may be a mechanical problem, with the vessels splinted open by fibrous adhesions formed as a result of the patient's original pathology, or it may be that the alpha-adrenoceptors are poorly responsive, possibly on account of the release of vasoactive substances or toxins produced during tamponade. Chernow (1985) has postulated this type of mechanism based on a theory described by Berridge and Irvine (1984) and future pharmacological developments in alpha-receptor modulators may elucidate its importance.

Although all these patients died eventually, none died with the ventilatory complications, seen

previously in similar patients, which may have been the result of overtransfusion. Two further patients have been managed along the lines described above. The data on these patients are incomplete, but both survived to be discharged from the Intensive Care Unit and, in particular, neither had pulmonary complications resulting from fluid overload. The frequent pulmonary complications previously seen in these patients may have been the result of inappropriate treatment of hypotension with excessive blood transfusion following abdominal decompression. Although some volume replacement is necessary during such operations, vasoconstrictors may be required in addition.

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The prevention of renal impairment in patients undergoing orthotopic liver grafting by infusion of low dose dopamine

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Summary

Administration of low dose dopamine (2.0 µg/kg/minute) begun before surgery in patients undergoing liver transplantation decreases the incidence of postoperative renal impairment. Thirty-four consecutive patients in the Cambridge/King's College Hospital liver transplantation series were studied. Nineteen patients (21 transplant operations) received prophylactic low dose dopamine throughout the operative and early postoperative period, while 15 patients (15 transplant operations) received dopamine only when clinically indicated for incipient renal failure or as an inotropic agent. In the prophylactic dopamine group, only two transplant operations (9.5%) were complicated by renal impairment, whereas in the other group, 10 patients (67%) developed renal impairment ($p = 0.001$); of these, four developed acute renal failure (27%). Comparison of seven pairs of patients, matched for age, sex, diagnosis, operative blood loss and operative hypotension (one group receiving dopamine, the other not), revealed a significantly higher urine output in the first 24 hours and creatinine clearance 24-48 hours after surgery ($p < 0.05$) in those treated prophylactically. In view of these findings, we would recommend that consideration be given to the prophylactic use of dopamine in patients undergoing orthotopic liver transplantation.

Key words

Surgery; liver transplantation.

Complications; acute renal failure.

Inotropes; dopamine.

Patients undergoing orthotopic liver transplantation may develop impaired renal function during the operation or in the early post-operative period and occasionally require haemodialysis. This may be due to several interacting factors, of which major blood loss occurring in the peri-operative period appears to be the most important. Haemorrhage results in sympathetic

vasoconstriction, which mainly affects the afferent glomerular arterioles, with a fall in renal blood flow and consequent renal ischaemia. Septicaemia and the use of potentially nephrotoxic drugs, such as cephalosporins or aminoglycoside antibiotics (especially in combination with loop diuretics) and the immunosuppressant cyclosporin A,¹ may also be causally implicated.

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Dopaminergic stimulation may reverse this sympathetic vasoconstriction and so help prevent the renal ischaemia.² Dopamine hydrochloride in the dose range 2–5 $\mu\text{g/kg/minute}$ is a potent renal dopaminergic agonist and is commonly used to treat patients with incipient renal failure,³ so its administration prior to and during major haemorrhage would seem worthy of consideration. In this report we describe our experience with the prophylactic use of an infusion of dopamine 2 $\mu\text{g/kg/minute}$, in patients having orthotopic liver transplant operations; the drug was started prior to surgery and continued into the postoperative period.

Patients and methods

In an 18-month period, 34 patients were treated by orthotopic liver transplantation; three of these patients required retransplantation within the same period. One patient with primary hyperoxaluria and renal failure, who had a combined liver and repeat kidney graft operation, was treated electively with haemodialysis both pre- and postoperatively and was therefore excluded from further analysis. All patients received 10% mannitol 1 g/kg during the procedure and all were given benzylpenicillin, cefoxitin and tobramycin during the operation and for 48 hours postoperatively. For immunosuppression, prednisolone and azathioprine were used; oral cyclosporin A was introduced in the second postoperative week in order to avoid the renal and pulmonary toxicity associated with intravenous administration immediately after operation.⁴ Details of the anaesthetic and surgical techniques have been described previously.^{5,6}

Nineteen patients (21 transplant operations) received a low dose dopamine infusion of 2 $\mu\text{g/kg/minute}$, begun with the induction of anaesthesia and continued for 48 hours postoperatively (group 1), while 15 patients (15 transplant operations) did not (group 2). A patient who required retransplantation for chronic rejection 6 months after her first transplant operation was treated with dopamine prophylactically only during her second operation and so was included in both groups. During this period there was no formal policy about the use of prophylactic dopamine; the decision whether or not to use it was made by the consultant anaesthetist involved.

The peri-operative details of these two groups

were compared, as was the incidence of renal impairment defined as oliguria (less than 0.5 ml/kg/hour urine output) in the presence of an adequate central venous or pulmonary capillary wedge pressure and a urine/plasma osmolality ratio of 1.1:1.0 or less,⁷ or acute renal failure requiring haemodialysis. In accordance with conventional management, a dopaminergic dose of dopamine was begun immediately a patient in group 2 developed renal impairment.

To determine whether bypass support, which diminishes venous congestion during the anhepatic phase of the operation, had a beneficial effect on renal function, the results for the five patients in the dopamine-treated group in whom veno-arterial bypass⁸ was used and for the six patients in the untreated group in whom venovenous bypass⁹ was used, were compared with the remaining patients in their respective groups. Similarly, as we have previously shown that younger patients have better survival rates than older patients after liver transplantation,¹⁰ the renal function of those aged 21 years or under was compared with that of the older patients within each treatment group.

Six pairs of patients were matched for age, sex and diagnosis and as closely as possible for pre-operative weight, plasma creatinine concentration and intra-operative blood loss and degree of hypotension. One of each pair was receiving low dose dopamine. The one patient who required retransplantation for chronic rejection 6 months after her first operation was included as the seventh 'pair'.

Statistical analysis was by the unpaired Student's *t*-test, the Mann-Whitney U test and Fisher's test of exact probability where appropriate.

Results

The two groups of patients were similar with respect to age, sex, diagnoses, pre-operative plasma creatinine and operative blood loss (Table 1). In group 1, only two (9.5%) of the 21 transplant operations were complicated by acute renal failure. A 13-year-old female who had compromised renal function before operation, with a plasma creatinine concentration of 150 $\mu\text{mol/litre}$, required haemofiltration from 6 days postoperatively and haemodialysis from 13 days, while a second patient (a 46-year-old male) required haemofiltration from 2 days and haemodialysis from 10 days postoperatively.

Table 1. Renal function in 34 consecutive patients undergoing orthotopic liver transplantation from 1 May 1983–31 October 1984.

	Prophylactic dopamine*	No prophylactic dopamine*
Number of transplant operations	21	15
Number of patients	19 (7M:12F)	15 (6M:9F)
Age, years		
Mean (SEM)	29.7 (4.3)	34.5 (4.3)
Range	2–58	2–57
Diagnosis		
Biliary atresia	3	1
Inborn errors of metabolism	1	1
End stage liver disease:		
Primary biliary cirrhosis	5	4
Chronic active hepatitis	3	2
Others	6	3
Malignant liver disease	1	4
Operative blood loss, litres		
Mean (SEM)	9.5 (2.9)	7.3 (1.7)
Range	0.3–54.0	1.0–22.2
Pre-operative plasma creatinine (concentration, $\mu\text{mol/litre}$)		
Mean (SEM)	75.9 (6.6)	79.0 (4.8)
Range	45–150	46–102
Outcome		
Renal impairment at 2 weeks	2/21 (9.5%)	10/15 (67%)
Acute renal failure at 2 weeks	2/21 (9.5%)	4/15 (27%)

*One patient who was treated with prophylactic dopamine during her retransplant operation, but not for her initial operation, is included in both groups.

In contrast, of the 15 patients (15 transplant operations) in group 2 not electively treated with dopamine, 10 patients (67%) developed renal impairment, a statistically significant difference ($p = 0.001$). In three cases this occurred during the operation; one patient subsequently required haemodialysis from the sixth postoperative day; six patients required dopamine within the first 24 hours after operation and three of these required haemodialysis within the first postoperative week, while the remaining patient started dopamine during the second postoperative day.

The incidence of renal impairment in patients in whom bypass support was used was not significantly different from that in the remaining patients in their respective groups. Likewise, no difference was found when the results within the two treatment groups were analysed with respect to age.

When the results for the paired patients were compared, it was found that the volume of urine produced on the first postoperative day and the creatinine clearance in the period 24–48 hours after operation were significantly better in those patients who received prophylactic dopamine

than in those who did not ($p < 0.05$; Table 2). There was no significant difference between the pre-operative renal function, the operative blood loss or the lowest recorded systolic blood pressure in the two groups.

Discussion

This study suggests that the prophylactic administration of dopamine, begun prior to the onset of surgery, decreases the incidence of renal impairment postoperatively in patients undergoing liver transplantation. Furthermore, although the numbers are small, renal failure requiring haemodialysis or continuous arterio-venous haemofiltration occurred less often and much later when prophylactic dopamine was given. The problems associated with results obtained from a retrospective study are well known; however, the dramatic fall in morbidity and mortality associated with the continuing use of prophylactic dopamine has been maintained since the end of the study period and we could not now ethically consider a prospective study in these patients. The inclusion in this study of a

Table 2. Renal function in paired patients. The first patient in each pair was treated with prophylactic low dose dopamine.

	Pairs							Statistics
	1	2	3	4	5	6	7	
Patient number	166	164	159	157	170	162	117†	148b 148a†
Age (years)/sex	46F	46F	2M	17F	13F	52M	47M	11F
Diagnosis	PBC	PBC	BA	CAH	Hepatoma	AC		R SAHN
Weight (kg)	50	44	13.8	52	35	80	81	40 36
Pre-op. plasma creatinine (μmol/litre)	91	64	—	61	49	97	108	46 107
Blood loss (litres)	3.8	6.0	0.7	7.4	0.3	16.6	7.9	11.3 3.9
Lowest systolic BP (mmHg)	80	90	90	95	70	65-70	90	80 90
Urine output (ml)								
0-24 hours	1420	1700	720	1010	1530	2040	630	1190 370
24-48 hours	2710	1730	440	1850	1880	4480	150	1260 740
Creatinine clearance (ml/minute)								
0-24 hours	74	50	15	51	108	74	13	30 8
24-48 hours	64	39	11	103	94	129	1	23 10

* Required haemodialysis 72 hours postoperatively.
† Required dopamine 0-24 hours postoperatively.
PBC = Primary biliary cirrhosis; BA = biliary atresia; CAH = chronic active hepatitis; AC = alcoholic cirrhosis; R = rejection; SAHN = subacute hepatic necrosis.

matched pair group overcomes some of the difficulties associated with a retrospective study and tends to reinforce the conclusions drawn from the findings of the larger unmatched group.

The use of bypass to decompress the portal circulation and to maintain the systemic blood pressure and renal perfusion, made no difference to the frequency with which renal impairment occurred, contrary to the report by Starzl *et al.*⁹ Also, the patients' age did not appear to alter the incidence of renal impairment, in contrast to its effect on overall mortality, in which the older patients did less well.¹⁰

The introduction of cyclosporin A has improved immunosuppression following organ transplantation.¹¹ However, its use in the early postoperative period following liver transplantation is limited by its nephrotoxicity. This necessitates the use of azathioprine, with the hazards of marrow suppression, and of high dose steroid therapy, with the disadvantages of an increased risk of, and difficulty in, the diagnosis of infection and adverse effects on carbohydrate metabolism which make parenteral nutrition difficult. Preliminary studies have shown that intravenous cyclosporin A results in a marked decrease in renal blood flow (P.R. Powell-Jackson, personal communication) and it may be that simultaneous low dose dopamine infusion will prevent, or at least lessen, this decrease and thus reduce toxicity, thereby allowing earlier postoperative use of this agent. Furthermore, if severe cyclosporin A nephrotoxicity can be avoided initially, the chances of long-term kidney damage may be reduced. Recently, a patient who was treated immediately after operation with cyclosporin A, given through a central venous line, developed severe pulmonary toxicity, but the anticipated nephrotoxicity did not develop, possibly due to the continued administration of dopamine.

Care is necessary in the extrapolation of results from liver transplant patients to others, but it seems appropriate to treat patients undergoing surgical procedures in which major haemorrhage occurs (such as ruptured abdominal aneurysms or following polytrauma) and who may be at risk of developing acute renal failure, with a dopamine infusion at a rate of

2 $\mu\text{g/kg/minute}$ throughout the operative and immediate postoperative periods.

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Quality of axillary brachial plexus block

Comparison of success rate using perivascular and nerve stimulator techniques

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Summary

A perivascular catheter technique (PVT) and a nerve stimulator technique (NST) for axillary brachial plexus block were compared in terms of quality: complete, incomplete or failed blocks. In a randomised series, 30 PVT blocks and 30 NST blocks were performed by three staff anaesthetists. In the NST group, surgical anaesthesia was always achieved, whereas in the PVT group, four blocks required supplementation with general anaesthesia. In both groups eight patients needed supplementation with additional conduction blocks of 1-3 peripheral nerves. It is concluded that a nerve stimulator technique may increase the success rate of axillary brachial plexus block to some extent.

Key words

Regional techniques; brachial plexus block.

It is believed that the use of a nerve stimulator to identify a nerve plexus provides an increase in both safety and success rate.¹⁻⁵ The perivascular technique for axillary brachial blocks,⁶ as modified by Selander,⁷ was used here for some 5 years, after which the method was replaced by the nerve stimulator technique. In a retrospective review of our results, surprisingly no difference was found between the quality of 200 blocks performed with the two different techniques. It was therefore decided to compare these two techniques under controlled conditions in a prospective study, in order to establish their efficacy.

Patients and methods

Sixty axillary brachial blocks for elective surgery were performed by three senior anaesthetists experienced in regional anaesthesia. In random order, half of the patients received an axillary

brachial plexus block *via* the perivascular technique with a catheter as described by Selander⁷ (PVT group). In the remaining patients, blocks were performed with the aid of a nerve stimulator in order to identify the axillary nerve plexus (NST group). No effort was made to distinguish between the three main nerve trunks. A Neurostim LA nerve stimulator, type 218 (Hugo Sachs Elektronik KG, FRG)⁸ and regional anaesthesia needles (50 mm, 22-G) with an electro-neurostimulation port (Vygon, France) were used.

Bupivacaine 0.5%, approximately 3 mg/kg, was given in a volume of 40 ml to patients weighing 50-70 kg, 50 ml for those 71-90 kg in weight and 60 ml for patients weighing over 90 kg. The volume was supplemented with physiological saline when needed.

Analgesia in defined areas of the ulnar, radial, median and musculocutaneous nerves was examined by pin-prick at 10-minute intervals, as

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Pharmacokinetic study of morphine in the postoperative period following liver transplantation: a preliminary communication

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Patwardhan and his colleagues (1) have shown that morphine does not have a prolonged effect in patients with severe cirrhosis, and this has led us to use morphine for postoperative analgesia in patients following liver transplantation. Small bolus doses and continuous infusion provide adequate analgesia, but have been associated with problems of prolonged narcosis in the Intensive Care Unit. These are exemplified by one particular patient, a 45 year old man who had undergone liver transplantation for malignancy. His early postoperative course was uneventful, and by the third postoperative day his liver function tests showed that bilirubin, alkaline phosphatase, SGPT, serum albumin and prothrombin time had stabilized. On the fourth day, his general condition suddenly deteriorated and he developed acute renal failure requiring hemofiltration and dialysis. He also required assisted ventilation, and the morphine infusion originally started for postoperative pain was continued for sedation purposes during ventilation. Over the next few days his level of consciousness remained depressed in spite of modest doses of morphine (24 mg/day). Despite the absence of miosis, blood was taken for morphine analysis on the 7th postoperative day. This was analyzed using a radioimmunoassay, and a plasma concentration of 600 ng/mL was found. Later that day, following dialysis, the plasma concentration fell to 250 ng/mL. The morphine infusion was continued as the results of the assay were not available for some time. Plasma morphine concentrations were measured several more times. These increased steadily over the next 2 days, despite no increase in the morphine infusion rate, reaching a maximum of 1200 ng/mL on day 9, at which point the morphine infusion was stopped. Following discontinuation of the infusion, plasma morphine levels decreased but even on day 11 a significant plasma concentration (200 ng/mL) remained. The decreases in plasma morphine levels appeared to be associated with the periods of dialysis but not hemofiltration. Our experience with this patient led us to study in more detail the kinetics of morphine following liver transplantation.

Methods

The surgical procedure of liver transplantation basically replaces the diseased liver with another. As part of the procedure a T-tube is positioned in the common bile duct so that bile

can drain externally. This operation can be associated with massive blood loss and considerable acid-base and electrolyte abnormalities. Patients were studied within two hours of their operation, once hemodynamic stability had been achieved in the ICU. Blood, urine and bile samples were obtained at regular intervals over the 24 hours after the morphine. Only a 2.5 mg dose of morphine, as a single i.v. bolus, was used because of the previous problems we had encountered. It was injected over a one minute period into a venous line. Specimens were analyzed for morphine concentration using the radioimmunoassay method described by Moore and colleagues (2).

Results and Discussion

Five female patients, aged 22-49 years (mean 35 years), weight 36-65 kg (mean 51 kg), have completed the study. Three patients had a diagnosis of primary biliary cirrhosis, one patient had fulminant hepatitis A, and one patient underwent retransplantation due to rejection. Table 1 shows the biochemical parameters, and indicates that all the patients had impaired liver function but normal renal function. The period of time the donor liver was hypoxic (ischemic time) is also shown.

Table 1

Biochemical parameters and hepatic ischemia time in five patients undergoing liver transplantation

Patient	Bilirubin (2-17 umol/L)*	SGPT (110-1000 U/L)	Prothrombin Time (seconds above normal)	Alkaline Phosphatase (30-135 U/L)	Creatinine (35-125 umol/L)	Ischemic Time (min.)
AM	98	297	4	91	<100	260
AB	180	1000	5	452	<100	174
JT	268	384	5	150	<100	297
BG	138	99	2	159	<100	279
DW	470	110	4.5	145	<100	359
Mean	230.8	378	4.1	199.4	<100	273.8

*Bracket value refers to the normal range.

The plasma morphine levels for each patient are shown in Figure 1. The normal sharp rise of morphine levels is evident. However, instead of the usual exponential elimination curve, a double peak pattern was evident in some of the patients. Such a pattern has been observed in other studies (3,4), and may be the result of enterohepatic recirculation (5) or simply an artifact. However, in these patients enterohepatic recirculation is unlikely with the external drainage of bile. This second morphine peak, occurring at 4 to 5 hours postoperatively, does not appear to be associated with any of the clinically apparent events. Urinary morphine and metabolites follow the same double peak pattern.

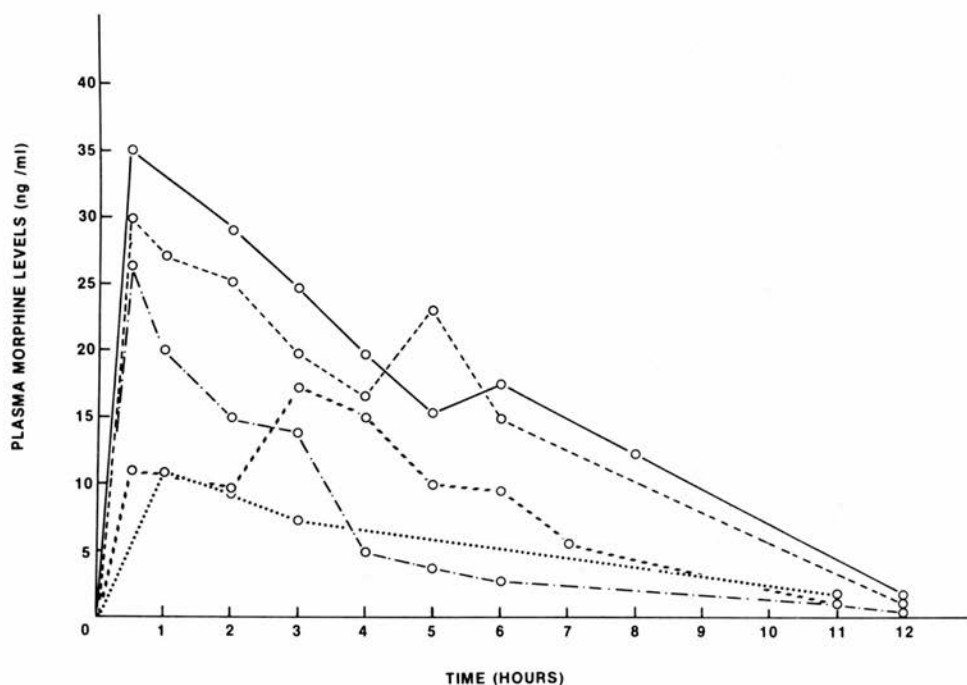


Figure 1. Plasma morphine concentrations in 5 patients following single i.v. doses of morphine administered 1-2 hours following liver transplantation. (Reprinted by permission of *The Lancet*)

One patient was particularly interesting. This was a woman of 49 years who had undergone liver transplantation for primary biliary cirrhosis. She was studied as per protocol on the first postoperative day and subsequently had a stormy course, with intercurrent sepsis and development of renal failure requiring dialysis and continuous arteriovenous hemofiltration. During the first investigation, her hepatic function was impaired but renal function was normal (serum creatinine was less than 100 $\mu\text{mol/L}$, urea 6.8 mmol/L , and urine output of 2600 mL over 24 hours). She was re-studied using the same protocol on the 30th postoperative day, at which time her liver function was improved but renal function was minimal - necessitating dialysis (creatinine 390 $\mu\text{mol/L}$, urea 73.4 mmol/L and urine output over the 24 hour study period of 100 mL). Her plasma morphine levels on the two study days are shown in Figure 2. The double peak is again evident, but on the second day levels were considerably higher despite use of the same 2.5 mg i.v. dose of morphine (6). Also, there was a peculiar lack of morphine elimination beyond 12 hours post-dose. We are puzzled as to the reasons for this unusual pattern, but it may support the evidence of others for a greater role of the kidney in morphine elimination (4). Its importance is clinically obvious, in that patients with renal failure may behave abnormally when given relatively low doses of morphine, but the extent and exact mechanism will require further study.

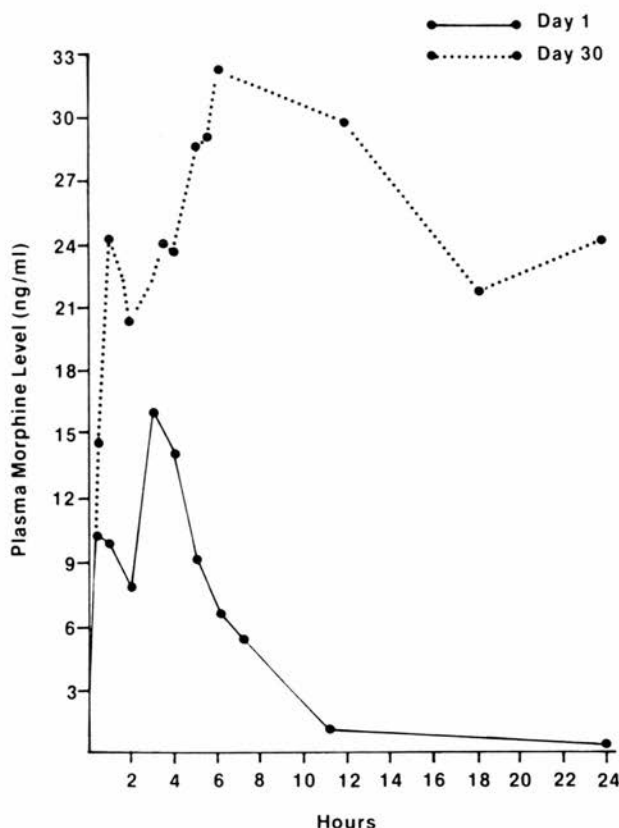


Figure 2. Plasma morphine concentrations in a liver transplant patient following single 2.5 mg i.v. morphine doses. On Day 1 the patient had normal renal function but impaired liver function. On Day 30, liver function had improved but renal failure requiring dialysis had occurred. (Reprinted by permission of The Lancet)

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oxygen. Saphenous vein grafting to the left anterior descending and right coronary arteries was uneventful. The patient was cooled during this procedure to 27 °C when cardiopulmonary bypass commenced and rewarmed to 37 °C before weaning from the pump.

His progress was complicated 3 days postoperatively when he developed an exacerbation of upper limb weakness, the right being more affected than the left. This weakness coincided with a lower urinary tract infection and associated pyrexia of 39 °C. Removal of his indwelling urethral catheter and antibiotics led to a resolution of his temperature. Three weeks post-operatively he had regained his pre-operative levels of function.

Deep induced hypothermia led to no exacerbation of the signs or symptoms of multiple sclerosis. Transient postoperative neurological deterioration was associated with a known aetiology - pyrexia.² Other possible sources of upper limb weakness such as over vigorous sternal retraction³ or traumatic cannulation of the right internal jugular vein⁴ may be excluded because of the late onset and relatively short episode of exacerbation of the limb weakness.

Coronary artery bypass grafting should be offered to patients with ischaemic heart disease who would normally warrant it. Some have been excluded in the past because of concern over the possible consequences of marked hypothermia and cardiopulmonary bypass on their multiple sclerosis. Avoidance of postoperative temperature elevation should be energetically pursued.

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Cell-saver

Dr Kumar's letter, (*Anaesthesia* 1986; 41: 774-5) was interesting. The Haemonetic Cell-saver is a type of autotransfusion blood salvage unit which is not really suitable for very rapid, massive blood loss. It is what I consider to be a slow autotransfusion technique. Other slow techniques are the Receptal system (Abbott Laboratories, Queenborough, Kent) and the Solco-trans (Cobot Ltd, High Wycombe). These techniques are useful when the blood loss is slow enough to be replaced by crystalloid or plasma substitutes. However, the Cell-saver produces the highest quality salvaged red cells and one can, of course, also recover other cellular components. Really large, rapid blood loss can only be salvaged and replaced immediately using the Bentley ATS system (Bentley Laboratories, Ilford), which uses a roller pump or a similar device¹ made up of standard cardiothoracic unit supplies. Very large blood loss of several litres/minute can be

recovered and immediately replaced with this roller pump system. It has the disadvantage, as does the Cell-saver, that it requires technical personnel to run it safely. It does, however, have the advantage that since the blood is salvaged immediately from the wound and passed straight back to the patient in a closed loop, Jehovah's Witness patients often accept this form of autotransfusion rather than others which involve some break in the loop.

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Reference

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Lack of haematological and biochemical consequences following autologous blood transfusion

The use of autologous blood transfusion during surgical operations is becoming established practice when major haemorrhage is expected. This technique is useful when stored blood is difficult to obtain because of shortage, incompatibility or rapidity of the bleeding; it may also diminish the risk of viral cross infection. Various authors have reported on the efficiency of such methods as the red cell-washing¹ (Cell-saver, Haemonetics, Natick, MA, USA), whole blood recycling systems² (the Sorenson

receptal device, Sorenson Research Corporation, Salt Lake City, Utah, USA) and the autotransfusion system³ (Bentley Laboratories, Irvine, CA, USA).

We have been using an automatic system (Haemonetics Cell-saver) during liver transplantation which, following the collection of blood from the operative field, heparinises it, then separates the red blood cells by centrifugation, washes and resuspends them in saline with a haematocrit of 60%.¹

There is controversy in the literature over the existence³ or not⁴ of a coagulopathy due to heparin which is re-infused with activated clotting factors. Any abnormalities that do exist should be particularly apparent in patients following liver transplantation in whom impaired liver function limits the body's ability to inactivate heparin and activated clotting factors. Liver function is impaired during liver transplantation, at the beginning when the recipient's own liver is being skeletonised, during the anhepatic phase and for several days after re-implantation of the donor liver when recovery from the ischaemic damage sustained when the liver was extracorporeal, occurs. Haemorrhage can occur intra-operatively during all of these phases, due to adhesions following previous surgery or division of anastomotic vessels. Bleeding is exacerbated by the portal hypertension and coagulopathy. In addition, the infusion of large amounts of washed red cells suspended in 0.9% saline may lead to biochemical abnormalities such as hypernatraemia and hypokalaemia.

The intra-operative biochemical and haematological changes of cell-saving systems⁵ and liver transplantation⁶ have been described separately, but little attention has been given to postoperative effects. Blood loss and administration details of 20 patients are shown in Table 1.

Immediately on admission to the intensive care unit after liver transplantation routine investigations are performed on arterial blood (Table 2). The patients had all received a similar amount of stored (citrate, phosphate, dextrose and adenine) blood intra-operatively. Ten of these patients had received, in addition, between 0.67 and 4.3 litres of cell-saved red blood cells. No statistically significant differences were found between

Table 2. Investigations performed on the two patient groups

Investigation	Cell-saved group mean value (SD)	Non cell-saved group mean value (SD)
Biochemical		
Hydrogen ion (mmol/litre)	36.4 (5.95)	34.2 (4.91)
Base excess (mmol/litre)	2.7 (4.79)	2.3 (5.09)
Potassium ion (mmol/litre)	3.2 (0.48)	3.0 (0.52)
Sodium ion (mmol/litre)	136 (3.59)	137 (4.07)
Glucose (mmol/litre)	20.7 (9.86)	14.7 (7.22)
Urea (mmol/litre)	9.8 (7.06)	6.0 (3.64)
Haematological		
Haemoglobin (g/dl)	13.8 (1.59)	13.4 (2.28)
Platelets ($\times 10^9$ /litre)	116 (54.49)	181 (85.43)
Prothrombin time ratios*	1.47 (0.19)	1.37 (0.15)
Partial thromboplastin time ratios*	1.45 (0.50)	1.15 (0.08)
Thrombin time ratios*	1.24 (0.15)	1.12 (0.14)

* Patient/control.

any haematological or biochemical variables between the two groups (Student's *t*-test).

The use of a red cell washing and re-infusion system of this type appears not to cause significant haematological or biochemical disturbances in patients following liver transplantation. It is therefore unlikely to cause significant changes in other groups of patients

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Table 1. Blood loss and administration details in ten patients who received banked blood only and ten patients who received banked blood and cell-saved blood.

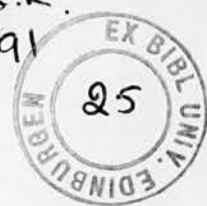
	Cell-saved group mean value (SD) (litres)	Non cell-saved group mean value (SD) (litres)
Total blood loss	7.4 (4.09)	4.5 (1.77)
Total transfusion (banked + cell-saved)	7.88 (3.08)	6.25 (1.32)
Banked blood	6.23 (2.63)	6.25 (1.32)
Cell-saved red blood cells	1.65 (range 0.67-4.3)	Nil

Safety hazard with cylinder yoke on a Boyle's machine

The following incident occurred recently and could have led to injury. A BOC International Mk 2 anaesthetic machine was in use, working from cylinders. One of the oxygen cylinders, having nearly emptied, was changed for a fresh one. This was offered up to

the yoke, the retaining bar was swung into place and the winged screw tightened in the usual way.

The cylinder valve was opened to check the pressure of the contents whereupon there was a sudden escape of gas at high pressure from between the valve and



PHARMACOKINETICS OF MORPHINE IN TWO CHILDREN BEFORE AND AFTER LIVER TRANSPLANTATION

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Morphine is metabolized by the liver (Stanski, Greenblatt and Lowenstein, 1978) and the metabolites excreted by the kidney. Recent advances in the estimation of morphine have, however, led to the emphasis being placed on the importance of its elimination by the kidney (McQuay and Moore, 1984a; Moore, Sear and Baldwin, 1984). Renal failure has long been known to prolong the action of morphine, and although this aspect has now been investigated further (Aitkenhead et al., 1984; Ball et al., 1985; Shelly and Park, 1985), the cause of the prolonged action remains obscure. In particular, the role of morphine metabolites has yet to be clarified. Morphine has a number of active metabolites, including morphine-6-glucuronide (Shimomura et al., 1971) and normorphine (Lasagna and De Kornfield, 1958; Johannesson and Milthers, 1962); the 3-glucuronide is thought to be inactive when administered parenterally (Sasajima, 1970; Shimomura et al., 1971). Initially, this was a pilot study to investigate the role of biliary excretion in the elimination of morphine, but we wish to report two patients who appear to illustrate the importance of the kidney in the elimination of morphine or its metabolites.

PATIENTS AND METHODS

Approval was obtained from the district Ethics Committee and informed consent was obtained from the parents of two children about to undergo orthotopic liver transplantation. Preoperative details are summarized in table I. Both children had end-stage liver failure unresponsive to other

SUMMARY

Plasma morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations were measured (HPLC) in two children immediately before orthotopic liver transplantation and in the postoperative period. Both of the patients had end-stage hepatic failure, but one also had impaired renal function before operation and was oliguric during and after surgery. Both patients metabolized morphine rapidly, but in the patient with renal failure, the metabolites appeared to accumulate. Morphine has active metabolic products and the accumulation of these in patients with impaired renal function may lead to a clinically observable prolongation of its effect.

medical and surgical treatment. One had congenital biliary atresia, the other cholestatic jaundice following neonatal hepatitis; both had secondary biliary cirrhosis. Renal function in both patients was thought to be normal in the preoperative period although, in retrospect, patient 2 had unrecognized renal impairment at this time: her

TABLE I. Details of two children before liver transplantation

	Patient 1	Patient 2
Age (yr)	3.5	2.5
Sex	M	F
Weight (kg)	14.0	7.5
Diagnosis	Congenital biliary atresia	Neonatal hepatitis + cholestatic jaundice
Bilirubin (mmol litre ⁻¹)	372	320
Alkaline phosphatase (mmol litre ⁻¹)	1430	2390
Urea (mmol litre ⁻¹)	2.2	12.1
Creatinine (μmol litre ⁻¹)	< 100	60

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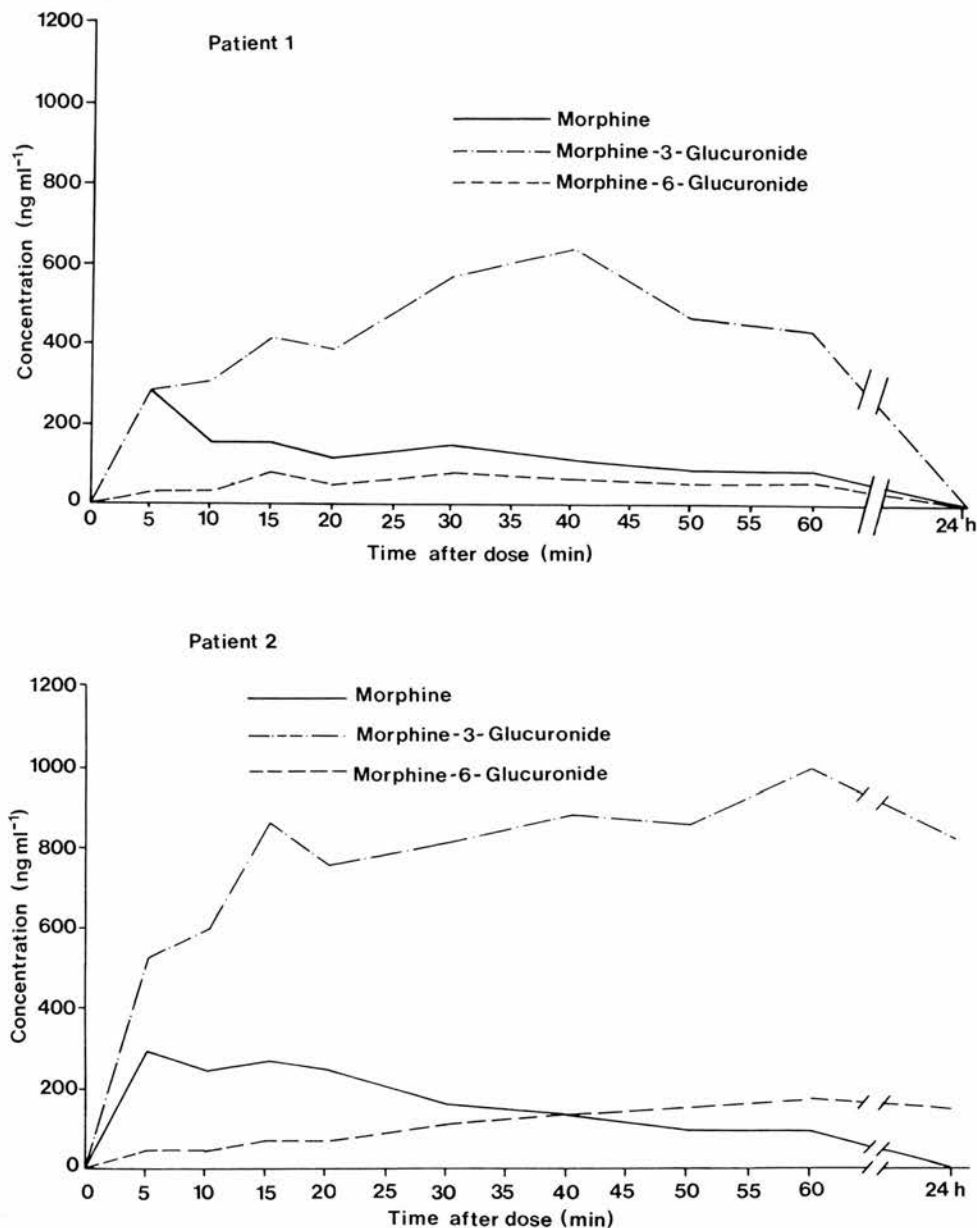


FIG. 1. Plasma morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations in patient 1 and patient 2 during the 60 min immediately before the start of surgery, and at 24 h after the administration of the morphine.

plasma urea concentration was increased although her plasma creatinine concentration was within normal limits.

Anaesthesia was introduced with thiopentone; alcuronium was given to facilitate tracheal intubation and controlled ventilation. Anaesthesia was

maintained with halothane and nitrous oxide in oxygen. Following the induction of anaesthesia, but before surgery, a blood sample (baseline) was taken and morphine 1 mg kg^{-1} was administered i.v. as part of the anaesthetic regimen. Further blood samples were taken at 5, 10, 15, 20, 30, 40,

50, 60 min after the administration of the morphine while venous access was secured and monitoring commenced—but before the start of major surgery. Blood removed for sampling was replaced by blood to maintain fluid balance. Further blood samples were taken from each child after surgery.

Plasma morphine, morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) concentrations were measured by high pressure liquid chromatography (HPLC). The standards used were morphine (Evans Medical Ltd, Beaconsfield) and M-3-G (Sigma Chemical Corporation); M-6-G was synthesized using a modification of the technique described by Yoshimura, Oguri and Tsukamoto (1968) and obtained through Napp Research Centre, Cambridge. Samples were prepared in control plasma for calibration, quality control and validation. Calibration curves were constructed for all three compounds.

Solid phase Bond Elut C18 cartridges (Jones Chromatography, Llanbradach, Glamorgan) were used to extract morphine and the two metabolites from plasma. Subsequent quantification was by HPLC using ultraviolet absorption at 210 nm to estimate M-3-G concentrations and electrochemical detection at +0.9 V (*v.* silver-silver chloride) to measure morphine and M-6-G. The lower limit of detection for M-3-G by ultraviolet absorption was 10 ng ml⁻¹ and for morphine and M-6-G by electrochemical detection was 1.5 ng ml⁻¹. Recovery from plasma for all three compounds was greater than 90%.

Pharmacokinetic parameters were determined using ESTRIP (Brown and Manno, 1978) to estimate terminal slopes. Clearance was calculated as dose (*D*) divided by the area under the curve (AUC) where AUC was estimated from the data points by the linear or logarithmic trapezoidal method and extrapolated to infinity. Volume of distribution at steady state was calculated as $D \cdot AUMC / AUC^2$ where AUMC is the area under the first moment curve, again extrapolated to infinity.

Clinical and biochemical indices of each patient's conscious level, and liver and renal function, as well as their opioid requirement, were recorded before and after surgery.

RESULTS

The plasma concentrations of morphine, M-3-G and M-6-G for both patients are shown in figure 1. During the first 1 h after the induction of

anaesthesia, but before the start of major surgery, the plasma concentration of morphine increased initially to high values and then decreased rapidly in both patients. The pharmacokinetic parameters of morphine were: in patient 1, half-life 0.4 h, volume of distribution at steady state 4.4 litre kg⁻¹ and clearance 93 ml min⁻¹ kg⁻¹; in patient 2, half-life 0.52 h, volume of distribution at steady state 3.4 litre kg⁻¹ and clearance 68 ml min⁻¹ kg⁻¹.

The plasma concentration of M-3-G increased in both patients, but more steeply and to higher values in patient 2. The concentration of M-3-G then decreased in patient 1, whereas it was maintained in patient 2. Plasma M-6-G concentration increased to a peak at approximately 15 min in patient 1 and was maintained at this value subsequently. In patient 2, however, the concentration of M-6-G increased gradually for the first 15 min, but continued to increase thereafter such that at the end of the 1 h the value was higher than that of the morphine base.

Patient 1, 24 h after his original dose of morphine, had no detectable morphine, M-3-G or M-6-G present in his plasma. Patient 2, 24 h after her original dose of morphine, had no detectable morphine base, but the concentrations of M-3-G and M-6-G were unchanged from concentrations measured at 60 min.

Intraoperative details for both patients are shown in table II. The duration of surgery and the blood loss were similar in both patients and both received a large blood transfusion. Patient 2, however, was anuric throughout the operation, whereas patient 1 had an adequate urine output.

The patients' postoperative urine outputs, conscious levels and opioid requirements are shown in figure 2. Patient 1 maintained a urine output of approximately 1 ml kg⁻¹ h⁻¹. He required the regular administration of fentanyl, in spite of which he remained difficult to sedate and further morphine was required 26 h after the initial dose to allow satisfactory control of ventilation. Patient 2 continued to have an

TABLE II. Operative details

	Patient 1	Patient 2
Duration of surgery (h)	5	5.5
Blood loss (ml kg ⁻¹)	79	80
Transfusion requirement (ml kg ⁻¹)	61	100
Urine output (ml kg ⁻¹)	6.0	0

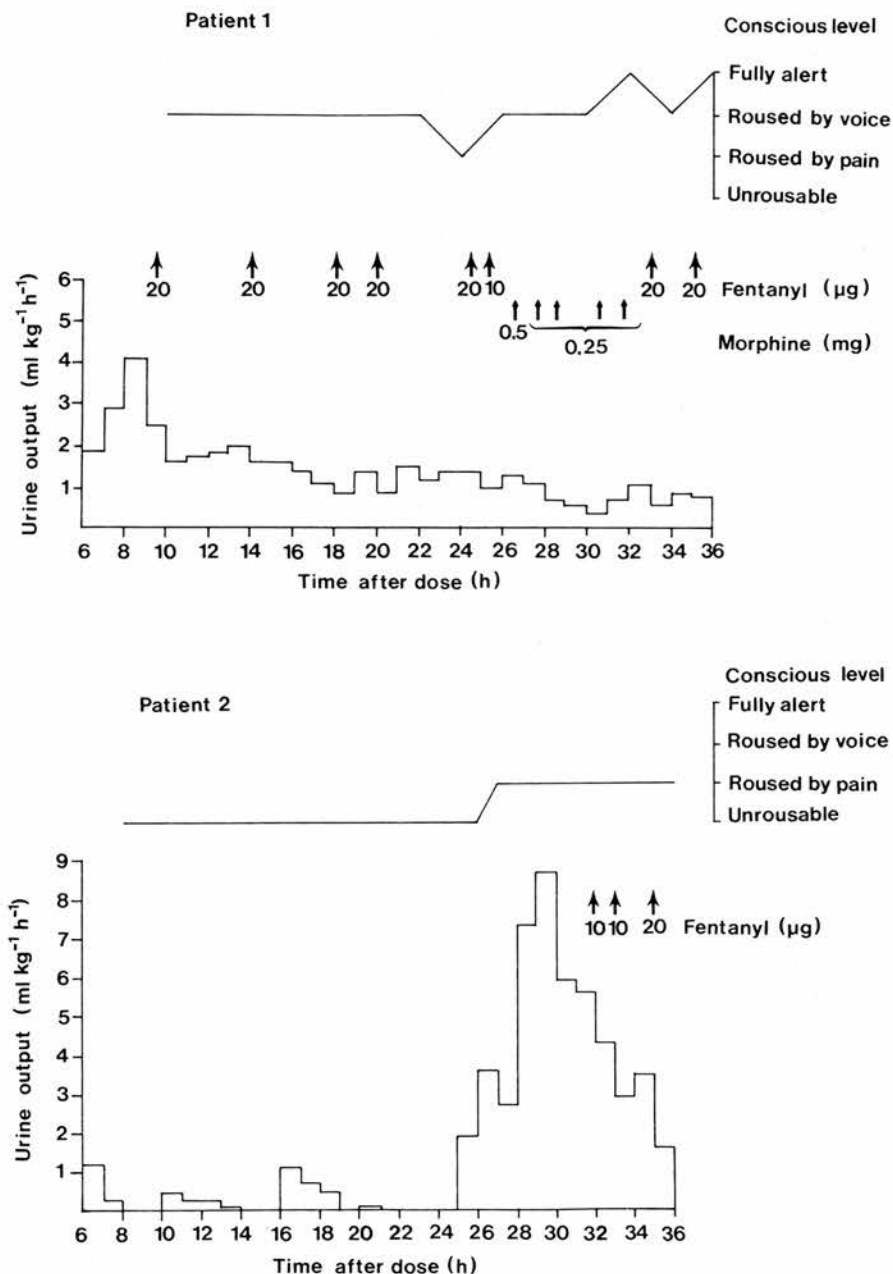


FIG. 2. Postoperative urine output, conscious level and opioid requirement in both patients.

inadequate urine output. In addition, although she received no further opioid, she continued to be unresponsive to painful stimuli and had pin-point pupils throughout this period.

Both patients started to produce bile promptly

after surgery and continued to do so, indicating reasonable recovery of liver function.

Patient 2 eventually responded to diuretic therapy and had a large diuresis. One hour after the start of her diuresis, she became responsive to

stimuli and her pupils enlarged slightly. Six hours later she required further opioid.

DISCUSSION

Although the liver has long been thought of as the site of morphine metabolism (Stanski et al., 1978), recently, patients with cirrhosis have been shown to eliminate morphine normally (Patwardhan et al., 1981). It has also been suggested that morphine is metabolized in patients with hepatic failure (Hug et al., 1979), but no details were provided of the assay method used to estimate the concentrations of morphine in that study. Extra-hepatic sites of morphine metabolism, such as the kidney (McQuay and Moore, 1984b) and the gastrointestinal tract (Park, 1985) have been postulated.

Both the patients described had liver failure during the preoperative period, yet both metabolized morphine rapidly; morphine concentrations decreased and the concentrations of M-3-G and M-6-G increased. Although neither patient was capable of producing bile at this time, the concentrations of morphine decreased. This may refute the importance of the biliary excretion of morphine.

The clearance of morphine in these children was greater than that previously reported in children (Dahlstrom et al., 1979). This may reflect the different methods used to estimate the plasma morphine concentration, or it may result from the relatively short sampling period available in our study before surgery was undertaken with the consequent haemodynamic instability.

The main differences between the two children were their renal function, and their plasma M-3-G and M-6-G concentrations. Patient 1 had normal renal function and had eliminated all detectable morphine, M-3-G and M-6-G by 24 h after the administration of the initial dose. Patient 2 had impaired renal function and a poor urine output. Morphine base was no longer detectable at 24 h, but high concentrations of M-3-G and M-6-G were present in spite of a large intraoperative blood transfusion to replace an operative blood loss approximating to her circulating blood volume. This accumulation of morphine metabolites would appear to indicate that an adequate urine output is important for their elimination. The clinical evidence of recovery in patient 2 when her diuresis started adds support to this hypothesis.

M-3-G is thought to be inactive parenterally, but M-6-G is known to be a powerful analgesic (Shimomura et al., 1971); however, its other actions are unknown. Patient 2 was unresponsive to pain and had pin-point pupils in association with the increased concentrations of M-6-G and this may indicate other opioid-like properties, particularly sedation. This assay method used was calibrated for only M-3-G and M-6-G. Other metabolites which may be active (e.g. normorphine) were not measured.

CONCLUSION

The two patients described illustrate that morphine can be metabolized rapidly, even in the presence of severe liver failure. Impairment of renal function with a low urine output in one of the patients was associated with accumulation of morphine-3-glucuronide and morphine-6-glucuronide and with prolonged narcosis. Morphine has active metabolic products and it may be these that produce the clinically observed prolonged action of morphine in patients with renal failure.

ACKNOWLEDGEMENTS

We thank Professor R. Y. Calne, Mr K. Rolles, Dr P. Morris and the staff of the anaesthetic department and the Intensive Care Unit at Addenbrooke's Hospital for their help with this study. We are also grateful to Dr G. F. Lockwood for his advice on the pharmacokinetic calculations and their interpretation.

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Severe hypercalcaemia due to a parathyroid-type hormone-secreting tumour of the liver treated by hepatic transplantation

We read with interest the paper by Dr Sealey (*Anaesthesia* 1985; 40: 170-7), and especially about the problems she encountered postoperatively. We have not been presented with a patient who has pre-operative hypercalcaemia, but it is interesting that several of our patients have suffered from late postoperative hypercalcaemia despite the use of prednisolone for immunosuppression. We have not yet explained this phenomenon, or seen it reported in the literature.

We have had similar difficulties in patients after liver transplantation, namely, hypoxaemia consequent on basal consolidation, difficulty in the provision of adequate analgesia and renal failure following heavy blood loss and cross clamping of the inferior vena cava. Recent changes in our management of these patients have alleviated some of these problems. Routine use of intermittent positive pressure breathing (IPPB) has markedly reduced postoperative basal collapse and subsequent consolidation. For the first 48 hours following extubation of the trachea, IPPB is administered from a Bird Mark 7 or Servo 900C ventilator, via a close fitting facemask, four times a day, along with intensive physiotherapy. Adequate analgesia is essential during this period but whilst the infusion of opiates is efficacious,^{1,2} we have seen considerable prolongation of, and sensitivity to, the effects of opiates in this group of patients. Our early pharmacokinetic studies suggest that, following liver transplantation, the metabolism or excretion of morphine occurs in a manner not previously reported. We therefore discontinue opiate infusions well in advance of weaning from ventilation and provide analgesia by intercostal nerve blockade, unless clotting is grossly deranged. Renal impairment (with a urine output less than 0.5 ml/kg/hour, a high right atrial or pulmonary capillary wedge pressure and a urine/plasma osmolality ratio <1.1) which previously occurred in 67% of our patients has been dramatically reduced to 10% by the prophylactic use of dopamine. A dopaminergic agonist dose (2 mcg/kg/minute) is used, starting prior to surgery and continuing for 48 hours afterwards (R. Poulson, G.R. Park, M.J. Lindop *et al.* unpublished).

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A reply

Dr Park and colleagues have raised a number of interesting points in the postoperative care of liver transplant patients.

Postoperative hypercalcaemia. Serum calcium levels are measured throughout operation in our patients and calcium chloride is given to maintain normal ionised levels. The need to give calcium falls sharply when the new liver is in place, is perfused and is metabolising citrate. In a series of 10 patients, which included the patient with preoperative hypercalcaemia, mean postoperative serum calcium levels were total calcium, 3.32 mmol/litre (range, 2.29-4.76) and ionised calcium 1.44 mmol/litre (range, 1.14-1.76). One patient and three patients respectively had normal levels. The duration of raised ionised calcium was a mean of 21 hours. This excluded those normal levels, and the 1.76 mmol/l result—that of the patient with pre-operative hypercalcaemia—which took 99 hours to return to normal. Late serum calcium levels in our patients have been unremarkable.

Analgesia and sedation. Patients are ventilated on an intermittent mandatory ventilation (IMV) mode, on return from theatre to avoid the use of muscle relaxants which make it very difficult to assess the effect of analgesic and sedative drugs, until they have warmed up from intraoperative hypothermia, are haemodynamically stable and arterial blood gas analysis and urine output are satisfactory. Hence it is important to explain to the patient what is going to happen in the intensive care unit and all are visited pre-operatively by the anaesthetist, the physiotherapist, and intensive care sister. It was not possible to explain fully to the hypercalcaemic patient reported on, what to expect in intensive care since the time course of his whole illness was very brief. This made management more difficult.

Analgesia is managed throughout the postoperative period (on an off the ventilator) by an infusion of opiate, usually papaveretum. The dose is limited to that required to keep the patient comfortable not to allow accumulation or untoward sedation: normal or less than normal amounts of opiate are required. No other sedatives are allowed, apart from a small dose of a benzodiazepine at night time, if necessary for sleep. We would be most interested to know the results of the Cambridge pharmacokinetic study but must stress that we find opiate infusion quite satisfactory if it is managed in the above manner and would be quite unhappy to use bilateral—for a bilateral subcostal incision—intercostal blockade.

Respiratory therapy. Physiotherapy in our patients is intense but does not routinely include intermittent positive pressure breathing. There are a number of factors which interfere with postoperative respiratory function: a large abdominal wound, abdominal disten-



PARK, G.R.
M.D. 1991
1100

THE LANCET, MAY 11, 1985

The synthesis and identification of this important metabolite will facilitate investigation of the specificity of antisera used in immunoassays, and thus confirm or refute the accuracy of current assays. In addition, since morphine-6-glucuronide may have analgesic activity greater than that of morphine itself,^{10,11} it may prove to be a useful therapeutic agent in its own right.

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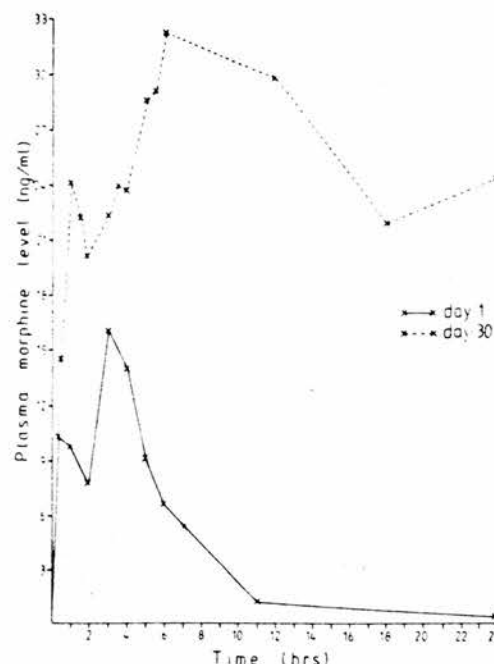
RENAL FAILURE AND USE OF MORPHINE IN INTENSIVE CARE

SIR.—We were interested in Dr Ball and her colleagues' comments (April 6, p 784) on the influence of renal failure on morphine clearance. We have described a patient with renal failure after orthotopic liver transplantation who was given a morphine infusion for postoperative analgesia and whose plasma morphine levels were very high.¹ This prompted us to study in more detail the pharmacokinetics of morphine in patients undergoing liver transplantation (and we hope to report on this later). Patients are investigated immediately postoperatively as soon as cardiovascular stability has been attained, usually within 2 h of returning to the intensive care unit. At this time their renal function is not impaired. Various doses of morphine are administered and plasma levels² are monitored for 24 h.

One patient, a 49-year-old woman with primary biliary cirrhosis, was studied in the immediate postoperative period, after a 2.5 mg dose of morphine. Renal failure subsequently developed and she was studied again one month later with the same dose. During the first investigation renal function was normal (serum creatinine below 100 µmol/l, urea 6.8 mmol/l, urine output 2600 ml in the 24 h period). On the second occasion her renal failure was controlled by arteriovenous haemofiltration and dialysis (creatinine 390 µmol/l, urea 73.4 mmol/l, 24 h urine output 100 ml).

Plasma morphine levels are shown in the figure. During the first study a peak 16.8 ng/ml was reached after 4 h and morphine levels returned to normal within 12 h. However, on the second occasion the peak was 32.2 ng/ml after 6 h, and morphine levels were above 20 ng/ml throughout the study.

The first study was done when the patient had good renal function but impaired liver function after an ischaemic period of 297 min. During the second study she was in renal failure but her liver function, apart from a raised bilirubin, was essentially unchanged. Although the pattern of results was similar on both occasions, during the second study the peak plasma level was almost double that of the earlier one and the half-life was much longer. The



Plasma morphine levels in patient after liver transplantation.

Day 1 = immediate postoperative study. Day 30 = patient in renal failure.

difference in peaks may represent a different volume of distribution, though the sustained high plasma morphine levels on the second occasion cannot be explained in this way. These results support Ball and colleagues' view that a renal mechanism for the clearance of morphine exists, despite the controversy over the assay method.³

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HYPOGAMMAGLOBULINAEMIA AND GASTRIC CANCER

SIR.—Dr Kinlen and colleagues (Feb 2, p 263) have suggested that the 50-fold increased incidence of stomach cancer in patients with common variable immunodeficiency (CVID) may be related to their high frequency of achlorhydria. However, they also point out that, since the excess of gastric cancer in patients with pernicious anaemia without immunodeficiency is less than 10-fold, other factors may contribute to the pathogenesis of gastric cancer in patients with CVID, such as an earlier onset of the atrophic gastritis or bacterial colonisation of the stomach in combination with the immune impairment.

We think that achlorhydria may not be crucial in the pathogenesis of stomach cancer in patients with CVID. Like others we have found that only about half of the patients with CVID are achlorhydric and even fewer have pernicious anaemia. Therefore patients with CVID and pernicious anaemia would have at least a 10-fold greater risk of gastric cancer than would patients with pernicious anaemia without immune impairment. This difference suggests that achlorhydria is not essential in the development of stomach cancer in patients with CVID. The finding that only half of the patients with CVID and stomach cancer are achlorhydric is also at variance with an important role for achlorhydria in the pathogenesis of gastric cancer in such patients.^{2,3}

in charge. There is adequate consultant sessional allocation for the purpose of running intensive care units but at the present time this sessional allocation is unknown. The patient is cared for jointly by the consultant who admits the patient, and the consultant in administrative charge of the unit. There is no approved training scheme for junior medical staff from any speciality for intensive therapy medicine. Anaesthetic trainees, however, can be expected to be exposed to intensive therapy during their General Professional Training. This, however, is a training requirement for all anaesthetists and takes no account of those few trainees who would like to undertake consultant sessional responsibility for intensive therapy units. These clearly need further training at Higher Professional Training level.

A recent very welcome development has been the establishment of the Inter-Faculty/Collegiate Liaison Group in Intensive Therapy. This was established on the recommendation of the President of the Royal College of Surgeons of England and the Royal Society of Physicians of England and the Dean of the Faculty of Anaesthetists. The remit of this group was to identify suitable posts at senior registrar (HPT) level in anaesthesia, medicine and surgery where one for one exchanges could be arranged to facilitate higher training in all aspects of intensive therapy. Candidates must have satisfied the requirements for accreditation in general (internal) medicine of the JCHMT; in anaesthesia of the JCHTA or in the appropriate surgical speciality of JCHST.

My personal hope is that the recommendations of the Inter-Faculty Collegiate Liaison Group will prove acceptable and additional funding found centrally for implementation of new rational training programmes open to trainees for all specialities.

Intensivmedizin: Organisation und Ausbildung – deutsche Aspekte

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Die Intensivmedizin in der Bundesrepublik Deutschland ist heute ein medizinischer Bereich, der von zahlreichen Disziplinen als integraler Bestandteil ihres Fachgebietes angesehen wird. Aus den operativen und konservativen Wachstationen der vergangenen Jahre haben sich inzwischen Einheiten der Intensivüberwachung, Einheiten der sogenannten fachspezifischen Intensivbehandlung und schließlich Einheiten der interdisziplinären konservativen oder operativen Intensivtherapie entwickelt. Die Einrichtungen der Intensivüberwachung sowie der fachspezifischen Intensivbehandlung stehen in der Regel unter Leitung des jeweiligen Fachvertreters, zumindest die operativen interdisziplinären Intensivtherapieeinheiten unter der Leitung des Anaesthesisten.

Nicht nur die großen Kliniken leiden heute unter einem Mangel an intensivmedizinischen Betten. Wurde ursprünglich von einem Gesamtbettenbedarf für den konservativen Bereich von 10% und für den operativen Bereich von 10% ausgegangen, so wird derzeit aus Kostengründen versucht, den Bestandteil der Intensivtherapiebetten einzufrieren oder gar drastisch zu reduzieren. Sogenannte Intermediäreinheiten, die zur Entlastung der Intensivbehandlungsstationen führen könnten durch solche Patienten, die noch nicht auf eine Normalstation

verlegbar sind, aber auch nicht mehr der Intensivbehandlung bedürfen, existieren nicht.

Seit Jahren besteht eine qualifizierte und programmierte Weiterbildung des Pflegepersonals, das in intensivmedizinischen Einheiten tätig ist. Es handelt sich um die Weiterbildung zur Fachschwester/Fachpfleger für Anaesthesie und Intensivmedizin, für innere Medizin und Intensivmedizin sowie für Pädiatrie und Intensivmedizin. Ein vergleichbar obligatorisches Weiterbildungsprogramm, das einen gleichmäßigen Standard auch im ärztlichen Bereich derjenigen Fachdisziplinen sichern würde, die intensivmedizinische Versorgungsaufgaben haben, existiert derzeit nicht.

Vielmehr bleibt es den Fachgesellschaften bzw. den Ärztekammern überlassen, den Mindestinhalt der Weiterbildung in den einzelnen Fachgebieten festzulegen und dabei auch den intensivmedizinischen Bereich angemessen zu berücksichtigen. Eine entsprechende Qualitätsverbesserung im ärztlichen Bereich in Anlehnung an den Pflegebereich erscheint dringend geboten.

Eine Entwicklung, die einen eigenständigen Facharzt für Intensivmedizin oder eine eigenständige Fachschwester/Fachpfleger für Intensivmedizin zum Ziele hätte, wird von den originären Fachgebieten mit intensivmedizinischen Versorgungsaufgaben nicht für erstrebenswert gehalten.

The Transplant Patient

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Cambridge is a unique centre in Great Britain with an active organ transplantation programme in two hospitals: Addenbrooke's Hospital (kidney, pancreas, cornea and liver) and Papworth Hospital (heart and heart/lung). Intensive care may be appropriate after any organ has been transplanted, but is essential following liver, heart and heart/lung. Not only are these long, complicated operations, but transplantation is only undertaken when end-stage organ failure has occurred resulting in a poor pre-operative state. The techniques and expertise developed to deal with the problems posed by the constant flow of such critically ill patients is of benefit to other patients needing intensive care.

Post-operative care following liver transplantation is challenging and may involve every aspect of intensive care. The early problems are a continuation of those encountered during the operation and include hypothermia, massive blood loss and rapid changes of plasma potassium and glucose [1, 2]. Problems occurring later include continued bleeding, renal failure, hypoxaemia, sepsis, rejection and nutrition. Some of these problems have been solved. Non-surgical abdominal bleeding has been controlled by the infusion of vasopressin when conventional blood component therapy has failed. The incidence of renal failure has been dramatically reduced by the administration of low-dose dopamine starting pre-operatively and continuing for 48 h. Hypoxaemia can result from several causes, including collapse of the lung bases. This has been prevented by the routine use of intermittent positive pressure breathing following extubation of the trachea.

Following transplantation, in particular that of the heart or liver, patients appear to be unusually sensitive

to narcotics [3], which may necessitate the use of regional anaesthesia.

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Therapie nach schweren Traumen

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Das posttraumatische kardiozirkulatorische Versagen (hämorrhagisch-hypovolämischer Schock) wird definiert als akutes Mißverhältnis zwischen Sauerstoffangebot und -bedarf des Organismus, was zu Störungen der Funktion von Zelle und Zellmembran, schließlich zum Zelltod führt. Ausgelöst wird dies durch eine schockbedingte, hypovolämische Verminderung des Herzzeitvolumens, was durch eine sympathico-adrenerge Reaktion kompensiert werden soll. Diese Reaktion ist durch Rezeptoren im Herz- und Gefäßsystem vermittelt und wird gegebenenfalls durch Hypoxie, Hyperkapnie und Azidose verstärkt. Die Stimulation adrenerger Alpha- und Beta-Rezeptoren führt zu schockspezifischen Veränderungen der Perfusion der Mikrozirkulation und letztlich zu einer Umverteilung des verminderten Herzzeitvolumens zugunsten vitaler Organe (Herz und Gehirn).

Übergeordnetes Ziel der Therapie schwersttraumatisierter Patienten ist die Wiederherstellung bzw. Sicherstellung der wichtigsten Organfunktionen. Speziell bedeutet dies die Aufhebung der Perfusionsstörungen der Endstrombahn. Nur so kann eine normale Durchströmung und Sauerstoffversorgung aller Organe gesichert werden. Die zunächst funktionelle Minderung der Funktion von Zelle und Zellmembran kann normalisiert, und ein Organversagen (Schocklungen, -niere, -leber) verhindert werden. Im Detail muß der pulmonale Gasaustausch gesichert werden – durch frühzeitige Intubation und Beatmung – das verminderte Blutvolumen normalisiert werden – durch Infusion kolloidaler/kristalloider Lösungen – und die Sauerstofftransportkapazität des Blutes muß angehoben werden – Transfusion von Erythrozyten – Kontraktilitätsminderung und Vasokonstriktion sollten durch positiv-inotrope Substanzen und Vasodilatoren therapiert werden.

Neueste Untersuchungsergebnisse zeigen, daß im traumatischen Schock dem Verlust von Funktionen der makro- und mikrovaskulären Gefäßendothelien eine wichtige pathophysiologische Bedeutung zukommt. Lange Zeit galt das vasculäre Endothel als eine weitgehend reaktionslose, tapetenartige Auskleidung des Gefäßsystems. In den letzten Jahren erwiesen sich Endothelzellen als hoch stoffwechselaktive Strukturen, denen wichtige Bedeutung zukommt. 1. Barriere-Funktionen, also die Abgrenzung des intra- und extravasculären Raumes, 2. Mitbeteiligung bei der CO_2 -Abgabe der Lunge, 3. Lokale und systemische Regulation des Gefäßwider-

standes, 4. Bildung einer antithrombogenen Gefäßoberfläche.

Besondere Bedeutung kommt im traumatischen Schock der Störung der physiologischen Regulation des lokalen Gefäßwiderstandes zu.

Vasodilatierende Wirkungen der vasoaktiven Stoffe werden – in regional unterschiedlicher Weise – durch eine Mediatorsubstanz des Gefäßendothels vermittelt. Dies kann nur die intakte Endothelzelle leisten.

Funktionsverlust des Endothels macht daher vasodilatatorische Einflüsse unwirksam. Daraus resultiert eine weitere, lokale Behinderung der Organperfusion. Dies hat im Gesamtablauf des traumatischen Schocks eine wichtige Bedeutung, ist aber derzeit therapeutisch noch nicht direkt zu beeinflussen.

Maschinelle Unterstützung der Atmung

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Während der letzten 15 Jahre haben sich die Prinzipien der maschinellen Unterstützung der Atmung wie folgt geändert: 1. durch positiven endexpiratorischen Druck (PEEP) und kontinuierlich positiven Atemwegsdruck (CPAP) und 2. durch die Möglichkeit, daß maschinell beatmete Patienten gleichzeitig auch spontan atmen können, entweder mit Hilfe eines kontinuierlichen oder eines Flow-of-Demand vom Beatmungsgerät. Historisch gesehen entwickelte sich dies aus der Kombination von Beatmungsgeräten, mit denen intermittierende Überdruckbeatmung mit PEEP möglich war, und kontinuierlichen Flow-CPAP-Systemen, die an ein vorhandenes Ventil, das dem Patienten die spontane Inspiration erlaubte, angeschlossen wurden. Diese neuen Möglichkeiten haben zu folgendem aktuellen Konzept der Unterstützung der Atmung geführt:

Volle Unterstützung der Atmung:

CMV = kontrollierte maschinelle Beatmung ohne oder mit PEEP oder CPAP

Partielle Unterstützung der Atmung:

IMV = intermittierende maschinelle/mandatorische Beatmung

Weiterhin hat sich auch der Entwöhnungsprozeß durch die Einführung von IMV geändert. Anstatt den Patienten von kontrollierter auf Spontanatmung direkt überzuführen, besteht jetzt die Möglichkeit, durch schrittweise Reduzierung der maschinellen Beatmungsfrequenz bis auf Werte von 2-0/min den Patienten zu entwöhnen, entsprechend seiner eigenen Fähigkeit, eine zufriedenstellende lungenmechanische und Blutgasfunktion aufrechtzuerhalten. Mit dem IMV-Konzept sind eine Reihe von Vorteilen verbunden, wie z.B. eine verminderte Notwendigkeit zur Verabreichung sedativer Medikamente und günstige Auswirkung auf Kreislauf und Nierenfunktion. Auf der anderen Seite ist der Patient unter IMV-Bedingungen stets dem Risiko einer inadäquaten maschinellen Unterstützung der Atmung ausgesetzt. Weiterhin gibt es technische Probleme mit IMV und CPAP. Kontinuierliche Flow-Systeme erlauben keine Messung der Beatmungs- und Atemvolumina, und einige der Demand-Flow-Systeme erfordern unerwünscht hohe und möglicherweise gefährliche inspiratorische Anstrengungen des Patienten, um den inspiratorischen Flow auszulösen.

advocated a skin excision margin one inch from the edge of the primary tumour with resection of an additional two inches of fat and deep fascia beneath the undermined skin edges; he also advocated resection of some muscle.

Dr Rampen's review is inaccurate in several other particulars. Day *et al* did not indicate that microscopic satellites were absent around lesions less than 1 mm thick—rather they wrote that no satellites were detected around 168 lesions of 0.75 mm or less thick; for 151 patients with 0.76-1.50 mm thick lesions 7/151 (4.6%) were found to have satellites.³ Furthermore, Elder *et al* indicated that they found no local recurrences in their patients (which they defined as reappearances of biopsy-proved melanoma within or contiguous to the definitive excision scar).⁴

Dr Rampen's analysis⁵ of the WHO study⁶ concluded that a 9.4% rate for local recurrence after excision of stage I melanomas with tumour free excision margins of 2 cm or less was unacceptably high. We have recently found in a minimum 10 year follow up study of stage I melanomas treated with conventional wide excision margins (most 5 cm or greater) that the rate of local tumour recurrence was 26/258 (10%).⁷ Not only should patients treated for melanoma be followed up for prolonged periods to determine the rate of local tumour recurrence, but the relative proportions of thin and thick tumours should be detailed as well as the surgical excision margins.⁸ Despite wide resection margins thick tumours are likely to be associated with an increased rate of local tumour recurrence, which will reflect simply the continuing growth of what were initially microscopic satellites outwith the margins of the resection—however wide they may have been.

The work of Day *et al*³ did indicate a 63% incidence of histologically proved microsatellites in the tissues surrounding melanomas greater than 4 mm thick, but they did not relate the position of these micrometastases to the margins of the primary tumour. We require to know the position of satellite lesions as well as their incidence in conventional wide margin excision specimens if we are to set out rationally recommendations on margins of excision for stage I malignant melanoma of the skin. A prospective randomised trial of varying excision margins related to primary tumour thickness and observed incidence of both micrometastases in adjacent tissue and eventual rate of local tumour recurrence over prolonged follow up is long overdue.

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of malignant melanoma. The American authors' argument runs as follows.

Local satellite metastases indicate that more widespread metastasis has already taken place. Excision of these local satellite metastases would therefore not eradicate the tumour and would be expected to have no effect on survival.

Surgical intervention can thus either eradicate lesions which have not metastasised (these tend to be "thinner") or at least allow histological assessment of prognostic features which may suggest that metastasis is likely to have already taken place and that surgery is already too late (these lesions tend to be "thicker"). In either case a wide margin of excision is unnecessary.

Adequate control of local disease by surgery may be important for cosmetic or psychological reasons where a cure cannot be achieved. For the same reasons it is important to avoid subjecting the patient to unnecessarily mutilating operations where no improvement in survival will result.

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1 Ackermann AB, Scheiner AM. How wide and deep is wide and deep enough? A critique of surgical practice in excisions of primary cutaneous malignant melanoma. *Hum Pathol* 1983;14:743-4.

Medical problems with breath testing of drunk drivers

SIR,—I was sorry to see the *BMJ* joining the *Daily Express* in publishing yet another letter (29 September, p 831) designed to cast doubts on the reliability of breath alcohol testing. The story it tells has already been repeated in the *Sunday Times* and carries a ring of authority as a result of having appeared in your columns. Like Dr Peter Duffus and Dr James A Dunbar, I occasionally receive such letters from hopeful solicitors, but this is one of the least convincing that I have read. In the first place, Dr Duffus and Dr Dunbar ignore one of the basic maxims in the business: "What the subject says he has drunk is not evidence."

The subject, on the other hand, seems to have been well briefed in the art of evading conviction. Taking a stiff whisky after an accident and before the police arrive is a well known ploy for confusing the issue and is illegal in many countries. Refusing a confirmatory blood test is another—rather new—ploy. Blood test results cannot be argued with, while breath tests as a result of the press campaign against them are only too easy to dispute.

The consultant gastroenterologist whose report got the subject off the hook was no doubt an expert in his discipline, but this was not breath alcohol. If stomach contents had reached the subject's mouth the breath concentration would have been much higher than 50 µg/100 ml because even diluted whisky has an alcohol concentration about a hundred times that of blood. The mouth concentration would fall rapidly so that the second sample would have given a much lower reading. The close agreement between the two readings is strong evidence that they were both recording true breath alcohol.

The Home Office is about to publish the results of an enormous blood/breath correlation study, and I have little doubt that these will be similar to those of its previous study which showed that not one out of 620 subjects would have been wrongly convicted on a breath test.¹

I hope, however, that the Home Office will continue the policy which I have always advocated, of allowing a blood test to anyone who wants it, and will not allow those who refuse it to dispute the breath test result.²

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1 Isaacs MDJ, Hunt DJ. *A survey analyses of breath and blood samples provided by subjects within the option range*. London: HMSO, 1984.

2 Wright BM. Breath test controls. Letter. *The Times*, 1981; 30 January.

* * A correction to the letter from Dr Duffus and Dr Dunbar is published on p 1080.—Ed, *BMJ*.

Children may still be harmed by a stay in hospital

SIR,—I must take issue with Minerva over a vital omission from her abstract (29 September, p 838) of Shannon's paper about children in hospital and subsequent behaviour problems.¹ Minerva concludes that "admission to hospital need not be seen as a risk to a child's later development," whereas the New Zealand group take pains to emphasise that their work was done "in an enlightened paediatric setting . . . where there is unlimited parental visiting and facilities for mothers to stay."

Figures from the recent Mitchell report on children in hospital in Scotland² show that of nearly 90 000 children discharged from Scottish hospitals in 1980 only 53% were from designated children's hospitals or departments. This leaves 47% being nursed in adult wards, where the state of paediatric enlightenment can be very far from ideal. As Mitchell comments, "a deplorable state of affairs."

The Mitchell report's other concern is with the size of paediatric units, advocating increased centralisation of resources into units of at least 50 beds. While our association participated in the preparation of the report and endorses its recommendations, we have two main fears about the way it might be implemented. Firstly, closure of local paediatric units may result in yet more children being admitted to adult wards. Secondly, insufficient emphasis may be placed on the problems of parents having to travel to more distant paediatric units and on Mitchell's recommendation that "parents must receive assistance to maintain the closest possible links with their children as of right."

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1 Shannon FT, Ferguson DM, Dimond ME. Early hospital admissions and subsequent behaviour problems in 6 year olds. *Arch Dis Child* 1984;59:815-9.

2 Working Group of the National Medical Consultative Committee. Scottish Home and Health Department. Scottish Health Service Planning Council. *Children in hospital: arrangements for inpatient care*. Edinburgh: HMSO, 1984.

Morphine toxicity with dilated pupils

SIR,—Dr Michael Nielsen and Dr John Henry (15 September, p 681) refer to using naloxone for the diagnosis and treatment of comatose patients with small pupils. While in the acutely poisoned patient pinpoint pupils and depressed consciousness and respiration are

SIR,—Dr F H J Rampen does less than justice to Ackermann and Scheiner¹ in his leading article on what constitutes adequate excision

1 Handley WS. The pathology of melanotic growths in relation to their operative treatment; I. *Lancet* 1907; i:927-33.

2 Handley WS. The pathology of melanotic growths in relation to their operative treatment; II. *Lancet* 1907; ii:996-1003.

3 Day CL, Harrist TJ, Gorstein F, *et al*. Malignant melanoma: prognostic significance of "microscopic satellites" in the reticular dermis and subcutaneous fat. *Ann Surg* 1981;194:108-12.

4 Elder DE, Guerry D, Heiberger RM, *et al*. Optimal resection margin for cutaneous malignant melanoma. *Plast Reconstr Surg* 1983;71:66-72.

5 Rampen FHJ. Melanoma of the skin: the problem of resection margins. *Eur J Cancer* 1981;17:589-90.

6 Cascinelli N, Van der Esch EP, Breslow A, Morabito A, Bufalino R. Stage I melanoma of the skin: the problem of resection margins. *Eur J Cancer* 1980;16:1079-85.

7 Griffiths RW, Briggs JC. Long term follow up in cutaneous malignant melanoma: the relationship of maximal tumour thickness to disease free survival, disease recurrence and death. *Br J Plast Surg* (in press).

8 Roses DF, Harris MN, Rigel D, Carrey Z, Friedman R, Kopf AW. Local and in-transit metastases following definitive excision for primary cutaneous malignant melanoma. *Ann Surg* 1983;198:65-9.

almost diagnostic of an opiate overdose, this may not always be the case. Two patients recently treated in this intensive care unit have had widely dilated pupils following a dose of narcotic sufficient to depress their consciousness and respiration.

The first patient had undergone liver transplantation and received a morphine infusion for postoperative pain relief and to facilitate artificial ventilation. On the ninth day after a stormy postoperative course (which included renal failure) concern was expressed over his conscious state. He had received 225 mg of morphine in this period and was still requiring artificial ventilation. His pupils were noted to be large. Despite this a sample of blood was taken for plasma morphine assay (measured by radioimmunoassay¹), and he was given several small doses of naloxone with improvement in his conscious level.

The second patient, who had a history of chronic renal failure, was admitted to the unit six days after a road traffic accident. He had received 510 mg of dihydrocodeine for pain relief during this six day period. He was unconscious and was intubated without the use of any drugs; respiratory depression was present, and his arterial carbon dioxide pressure was raised (7.11 kPa (53 mm Hg)). His pupils were noted to be dilated. Blood was taken for plasma morphine assay and analysed by the same method. He responded to 0.3 mg naloxone with an increase in conscious level and respiration (arterial carbon dioxide pressure falling to 4.84 kPa (36 mm Hg)) and was subsequently maintained on a naloxone infusion.

In both patients the plasma morphine concentrations were very high (1185 ng/ml in the first, 3963 ng/ml in the second), confirming the clinical impression of narcotic toxicity in the absence of small pupils. Renal failure may have contributed to the problems seen in both patients,^{2,3} and we hope to report them both in greater detail when further assays of blood and urine have been undertaken.

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- 1 Moore RA, Baldwin D, Allen MC, Watson PJQ, Bullingham RES, McQuay JH. Sensitive and specific morphine radioimmunoassay with iodine label: pharmacokinetics of morphine in man after intravenous administration. *Ann Clin Biochem* (in press).
- 2 Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose IV morphine in normal volunteers and patients with end stage renal failure. *Br J Anaesth* 1984;56:813.
- 3 Barnes NJ, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *Br Med J* 1983;286:438-9.

Apheresis procedures in polycythaemia

SIR,—Dr Terry Hamblin discusses the use of apheresis in treating various disorders (29 September, p 779), but omits consideration of the removal of red cells using a cell separator (erythrapheresis).

The technique has been used for some time for rapid red cell exchange in patients with sickle cell disease.¹ We have shown that in patients with primary polycythaemia and polycythaemia secondary to chronic hypoxic lung disease a single separation can reduce packed cell volume and blood viscosity to normal.² This avoids the inconvenience of multiple venesections and considerably reduces visits to hospital. The other main advantage of

erythrapheresis over other methods is safety; the red cells removed are replaced with an equal volume of iso-osmotic replacement fluid. This minimises any thrombocytosis or sudden changes in cardiac output.

While the advantages of such a rapid and effective technique in primary polycythaemia are self apparent (reducing exposure to radioactive phosphorus or cytotoxic agents) we have also shown that isovolaemic haemodilution has advantages in patients with chronic hypoxic lung disease complicated by secondary polycythaemia. After erythrapheresis in this group we have shown appreciable symptomatic improvement and increases in exercise tolerance and mental alertness with no complications related to the separations.³ Dr Hamblin emphasises the susceptibility of apheresis procedures to placebo effects. In a study comparing the effects of erythrapheresis with a sham apheresis procedure we found that this technique had no significant placebo effect with respect to changes in exercise tolerance.⁴

It is not feasible for every patient with polycythaemia secondary to lung disease to undergo erythrapheresis, and we do not recommend purchase of an expensive machine for this alone. We think, however, that those patients with severe polycythaemia in whom venesection would be required over a prolonged period and in whom any adverse haemodynamic disturbance is undesirable would benefit from, and should be considered for, erythrapheresis.

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Time to push aside the diagnosis of infantile colic

SIR,—The short report on infantile colic and parental smoking (15 September, p 660) prompts me to raise a more fundamental question—is there such a thing as infantile colic?

If one takes that term literally then I personally doubt it very much. There are some babies who cry incessantly for no apparent reason. Whether or not the origin of this is parental anxiety and insecurity, a vicious circle is created between the latter and the baby's crying. But I am often impressed that if the baby is removed from the vicious circle by admission to a paediatric ward the screaming or colic ceases. Affected infants do often later have a "difficult" temperament be it inherent or secondary to the environmental problem.¹

With emotions so charged it is hardly surprising that standard remedies should be thought to be effective. No studies yet show a statistically significant improvement with infants treated with dicyclomine, and any

claimed efficacy is probably due to its sedative rather than its antispasmodic action.

What harm can be done by using the label of colic when faced with a screaming baby? Firstly, some babies with such potentially fatal illnesses as meningitis are initially labelled as having colic. Secondly, the standard remedy dicyclomine has side effects which may occasionally be life threatening.² Thirdly, wrong advice is often given regarding cows' milk protein sensitivities, etc.

I thus feel that much would be gained if the diagnosis of colic was pushed aside to fester along with such old favourites as teething causing convulsions.

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Diazepam tolerance

SIR,—Dr P J Cook and others (11 August, p 351) give some results that differ from our findings with diazepam and the midazolam. Like them we found great variability in response to both drugs.^{1,2} Diazepam is slow acting, which causes problems with intermittent injections—particularly when they are given at one minute intervals. The onset time with midazolam varies indirectly with age,³ and on clinical grounds we believe this applies to diazepam. The important point is that older patients not only require less drug but are sedated more quickly than the young, who are often very resistant.

When giving a fixed weight related dose of midazolam we found a good positive correlation between rapidity of response and the percentage of unbound midazolam in plasma.⁴ Furthermore, in one large series of patients a direct relation was found between plasma albumin concentrations and rapidity of onset, thus emphasising the importance of plasma binding.⁵ The conclusions that Dr Cook and others draw from their figure 3 in relation to plasma binding are unjustified as the younger patients required more drug. It would have been more meaningful to give the free drug as a percentage of the total plasma diazepam.

One important omission is the name of the diazepam preparation used—since the soya bean oil emulsion formulation (Diazemuls) has a bioavailability up to 20% less than the standard organic solvent preparation (Valium).⁶ If these were given at random the findings are meaningless. The possible influence of cimetidine, which affects diazepam disposition,^{7,8} is also ignored.

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